

A Step in the Right Direction

THE first thing to be said about last week's statement on nuclear power policy by Mr John Davies, Secretary of State for Trade and Industry (see *Nature*, **238**, 303; 1972), is that it has removed some of the uncertainty that has shrouded the industry for the past twenty months. Britain is not to buy American pressurized water reactors immediately, even if the possibility of doing so some time in the next decade has not been completely ruled out. Also, the advanced gas cooled reactors are not to be condemned out of hand, and the high temperature reactor may yet be fully developed with help from the Germans.

Although the present government is most immediately to blame, the history of muddle about the British nuclear power industry goes back for the best part of two decades, to the point in 1955 at which the then government, acting on the advice of the Atomic Energy Authority and the Central Electricity Generating Board, decided to set up four consortia of industrial companies to construct the gas-cooled reactors which, it was then thought, would soon be springing up like mushrooms in Britain and in export markets abroad.

It is now clear, however, that the government's concept of partnership between the AEA and the CEGB and the industrial consortia was nothing like as equitable as it should have been. Between them, the public corporations remained responsible for research, development and a good deal of the detailed design of the reactors which have since been developed. The industrial consortia were torn by the sense of impotence which this arrangement gave them and the heady prospect of profitable sales without commensurate expenditure on innovation. But, in the event, the export markets have not materialized, new designs have succeeded each other more quickly than the domestic market could usefully absorb them, the number of consortia has shrunk from four to two as commercial prospects have dimmed and now a further amalgamation into one is promised. Throughout this period, the Atomic Energy Authority, technically as good as any comparable organization in the world, has been superbly confident of its judgement of what the market needs, and in spite of the unwillingness of the CEGB to buy reactors (such as the advanced gas-cooled reactor) which it thought it might not need, the result is that after twenty years and the expenditure of nearly as much on reactor development as on Concorde (which is an even less good bargain), nobody can be sure whether the British nuclear industry is now in a position to sell reactors successfully. For the past five years, it has also been apparent that there is a necessary connexion between the scale of nuclear research and development in Britain and the potential profitability of the market and, while some parts of the AEA have been reorganized—fuel manufacturing has been, for example, split off to British Nuclear Fuels Limited—the part of the AEA concerned principally with the development and design has

languished in an awkward limbo, unsure of its role.

The biggest conundrum left unsettled is how the government will arrange to subsidize those kinds of research and development which may, in the long run, be exceedingly important but which lie beyond the time-scales of organizations like that to be set up. To be sure, Mr Davies has promised £15 million for component design for the fast breeder reactor but presumably the government is going to have to continue subsidizing work like this for several years with a simple subvention for research and development. That is something that it must grit its teeth and bear. If there should be difficulties in a proposal that private enterprises should benefit by continuing injections of public money, they should be suppressed. But it is also essential that subventions of this kind should not be hand to mouth affairs but, rather, deliberate decisions validated against publicly declared plans for research and development which will last for the decade or so required to carry through long-term development. In short, the government should declare what might and should happen to the long-term development of nuclear power in Britain. The past few decades, it is true, have been a disappointment, but only a relative disappointment; it would be foolish to discard what has been done for the sake of a commercial principle.

The most serious drawback in the arrangements which the government now proposes is that the time may well have passed when the creation of large industrial consortia for building nuclear power stations is a sensible procedure. Public utilities are now much better placed than they were fifteen years ago to place orders for the separate components of a nuclear power station, with the result that the massive turnkey contracts of the past are likely to tail away. It is true that thoroughly competent design organizations may be able to function as consulting engineers used to do half a century ago, and plainly a central organization has the advantage that it may be used more effectively to administer safeguards and the continuing supply of fuel. It will be some time before anybody can guess how fully the British Government's new proposal for one large consortium meets this need.

The question of whether the immediate future—the next ten years—will see the building of nuclear reactors on the old-fashioned British style is more problematical, and the recent CEGB statement that it only foresees the need for at most four nuclear power reactors by 1982 has only clouded the issue, for predictions of power needs are notoriously unreliable. Whatever the type of thermal reactor the government and industry between them decide to build in the period before the fast breeder reactors become commercially available, few crocodile tears should be shed over the decision. If the government creates a viable industry by providing funding for the fast breeder reactor, then the frustrations of the past few years will soon be forgotten.



Privacy and Transplants

In the past few years, transplant surgeons of all kinds have complained that excitement and sometimes exaggeration in the newspapers have frequently hampered their work. It appears, for example, that the supply of kidneys for transplantation diminishes at least temporarily whenever newspaper readers are being regaled with exciting accounts of how a dying person is rushed across the centre of a city, with a police escort in attendance, and when the relatives of the people concerned, the recipient of a heart transplant or the unfortunate donor are interviewed for publication. What seems to happen is that the relatives of possible donors for kidney operations, now a part of routine medical practice, shrink from giving their consent to the operation for fear they, too, will be harassed by journalists at what is bound to be a distressing time for them. The consequences are serious because the supply of kidneys is not nearly great enough to meet the growing demand, which is why some surgeons have come to resent the interest of the newspapers in transplant operations and, worse still, have sometimes attempted to deny them information. Nobody will pretend that the question is an easy one, which perhaps explains why it has been dealt with somewhat superficially in the *Report of the Committee on Privacy* under Mr Kenneth Younger which has now been published (Cmnd 5012, HMSO, £2.00) and on which the British government promises to take action in the next parliamentary session.

Transplant operations are genuinely of public interest and there is no cause for denying journalists full information about them. That is the first thing to be acknowledged. Not merely does the public have a right to know what kinds of operations are being undertaken but it is also important that medical people should not be the sole custodians of information about the personal circumstances of donors and recipients. Especially when some forms of transplant operations are necessarily difficult and rare, it would, for example, be a matter of great public interest if they were performed exclusively on wealthy recipients, or if the beneficiaries were in some other sense privileged. Similarly, the public needs to know that the circumstances in which organs are taken for transplantation are seemly, that the donors are selected carefully and that their relatives have been properly consulted. It follows that newspaper journalists should be given full information about all transplant operations in which matters of public interest are, in their view, involved. The question is whether it is then possible to arrange that the information can be dealt with in such a way as not to embarrass the families of those concerned. The fact that one consequence may be a diminution in the supply of kidneys for transplantation is only part of the problem—it is in general intolerable that the family of, say, a donor should be exposed to public gaze unless, for some reason of their own, they have no objection.

The Younger committee includes a brief discussion of the publicity surrounding two heart transplant operations in Britain in 1969 and 1970. It quotes evidence given by the Press Council that the publication of the identity of donors and recipients was a necessary part of establishing the authenticity of the news as well as an invaluable means of creating a sense of immediacy and of personal

involvement among newspaper readers. On balance, the Younger committee takes the view that the Press Council has exaggerated the importance of the freedom of newspapers to publish the names of those involved in transplant operations and it goes on to recommend that the Press Council should draw up a summary of its previous adjudications on subjects like these so as to provide a more convenient framework within which journalists, if they choose, can elect to work. This is not enough. The Press Council, after all, has no power to regulate the way in which newspapers and other journals function.

So would it not be sensible to consider a legal prohibition on the publication of the names of donors and recipients in transplant operations unless the people and relatives concerned had given their consent in writing? Beneath the umbrella of such constraint, it would be much easier than it is at present for hospitals to give full details of transplant operations to journalists, and for the latter to investigate as fully as they chose the circumstances in which particular transplant operations have been carried out. And although it might often seem that a full description of the circumstances might serve to identify the people concerned, these are problems with which the newspapers contend already in other fields—in the reporting of the proceedings of juvenile courts, for example, where the names of those charged with offences must not be published and where it is for newspapers to ensure that they do not unwittingly reveal the identity of the person concerned by too full a description of the circumstances. Although it will be unwelcome to most people that there should be further restrictions on the freedom of the press to publish, the British government should seriously consider a legal restraint on publication of the identity of those involved in transplant operations, coupling it with an obligation on hospitals to provide access to information. And the principle might well be extended to other novel forms of operation, many of them still around the corner—the transplantation of fertilized eggs into the human uterus, for example.

100 Years Ago



DR. HAYDEN, in charge of the Geological Survey of the Territories, having completed his preliminary arrangements at Ogden, has separated his forces into two divisions, one of which was to proceed to Fort Hall, with waggons and a suitable outfit, to be changed into a pack train at Fort Hall, and thence to travel up the Snake Valley, under the direction of Mr. Stevenson; the other division, under the doctor's own charge, was to start soon for Fort Ellis, and expected to be at work there by the 1st of July. Among other interesting observations already made by Dr. Hayden's expedition, was the occurrence of invertebrate animal life in great abundance in the Great Salt Lake. This fact is not entirely new, as the existence of dipterous larvæ in these waters has already been recorded by Captain Stansbury and others.

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OLD WORLD

Scientific Community Rises to the Occasion

YET another storm is brewing over the treatment of scientists in the Soviet Union. It was reported last week that Professor B. G. Levich has been deprived of his university chair at the University of Moscow and that he has also been removed from his position as head of the theoretical department at the Institute of Electrochemistry in Moscow.

The persecution of Professor Levich started in March of this year when his two sons and their families applied for certificates of good character as a preliminary to their application for permission to emigrate to Israel. Soon after this the staff at Moscow University recommended that Professor Levich be dismissed from his position, a recommendation which the university authorities soon implemented. The reason given to Professor Levich for his dismissal was that the decision of his sons to emigrate to Israel showed that the moral influence of their father was less than desired and that he was therefore unsuited to teaching.

Following this, Professor Levich applied to the Academy of Sciences for a certificate of good character so that he himself could emigrate to Israel and as a result he was removed from his position as head of the department and was made a senior scientific worker—a much lower grade and a position that does not entitle him to receive applications to attend conferences or to have any scientific contact with his pupils or colleagues. Professor Levich was informed on June 12—orally by Academician Frumkin, head of the Institute of Electrochemistry—that his application to emigrate to Israel had been turned down.

Since April Professor Levich, according to all accounts, has been unable to lecture, and all enquiries from abroad either go unanswered or the enquirer is informed that Professor Levich's colleagues no longer wish to work with him or hear from him.

The persecution has not been limited to Professor Levich himself, for his sons have suffered as well. Last week it was learned that Evgeny Levich, who works in the Academy of Sciences, has been called up for military service even though he suffers from a serious blood pressure condition. The other brother, Alexander, lost his job as a corrosion engineer in March and found great difficulty getting another.

Professor Levich's plight has not gone unnoticed in Britain, and at the beginning of August an appeal was launched by Sir Derek Barton (Hofmann Profes-

sor of Chemistry at Imperial College, London), Professor K. G. Denbigh (Principal of Queen Elizabeth College, London), Sir Frederick Dainton (Dr Lees Professor of Chemistry, University of Oxford), and P. V. Danckwerts (Professor of Chemical Engineering, University of Cambridge), "to assist in regaining full freedom of work, publication and movement for Professor Levich".

Within two and a half weeks of the launch of the appeal 250 signatures have been received by the sponsors. The aim is to publish repeatedly in journals which circulate within the Soviet Union

a list of the supporters of the appeal which the sponsors hope will be longer each time. The hope is that, in this way, the Soviet authorities will bow to the pressure of world wide scientific opinion and either restore Professor Levich to his former positions or grant him permission to leave the country.

Sir Frederick Dainton said this week that he had offered Professor Levich a position at the Physical Chemistry Laboratory at Oxford for a year, but discovered after telephoning Levich that he had not received the offer. Sir Frederick emphasized that the offer to Professor Levich was made on the

NRDC

Report Suppressed

THE National Research and Development Corporation (NRDC) has opted to suppress a critique of its selection and control procedures undertaken by the Centre for the Study of Industrial Innovation (CSII).

The study was run late last year by the CSII after Mr Patrick Docksey's inquiry into NRDC's machinery on behalf of the Department of Trade and Industry. The centre agreed that the study should consist of two parts, the first a preliminary survey to examine the way in which the NRDC selects the projects it backs and the way in which it then controls them, to be followed by a fuller study of case histories to prove or disprove the conclusions of the preliminary study. It was always understood that the second part of the project might not materialize and that the CSII might not be able to publish the results of its study, although, being an independent research organization with a view to informing the public about the problems of innovation, it presumably hoped that publication would be possible. CSII produced its first report early this year after three months' work. NRDC examined its conclusions and decided not to proceed with part two of the exercise and also would not allow CSII to publish the report. This week the corporation declined to comment on its reasons for not proceeding with the study.

The conclusions of the CSII study are well guarded—the researchers had to sign the Official Secrets Act before beginning work—but it is no secret that the centre's conclusions differed somewhat from those of Mr Docksey.

Some of Mr Docksey's conclusions have already been aired, both by Mr Michael Heseltine, minister responsible

for the NRDC at the Department of Trade and Industry, and by Mr Docksey himself before the Select Committee on Science and Technology (see *Nature*, **238**, 182; 1972). Further details of his views will become public shortly when the DTI, following intense pressure from the select committee, publishes his report. Lord Jellicoe, Lord Privy Seal, informed the committee recently that Mr Docksey's report would be made available to the committee, and Mr Airey Neave, chairman of the select committee, said this week that he hoped to receive a copy—with confidential material suitably edited out—within the next week or two. He has been assured that general publication will follow shortly.

But whatever embellishments Mr Docksey's report adds to what is already known of his views—and by all accounts the report may prove to be a damp squib—it is apparent that both the NRDC and the CSII may disagree strongly with his views.

Meanwhile the CSII is facing something of a financial crisis. Industry provides the centre with support to the tune of about £7,000 a year, and the centre earns itself about the same amount in contract research on innovation. It is proving increasingly difficult, however, to make ends meet, and the centre is shortly to apply to the Social Science Research Council for a grant of between £5,000 and £7,000 a year over three years to help it keep going. A decision will not be reached until the end of the year, but the centre can remain solvent until the spring of 1973 without immediate aid. Its chances of obtaining a grant must be reasonably strong as the National Institute for Economic and Social Research, a body working in a not dissimilar field, was awarded a five year grant of £277,000 by the SSRC in 1968.

basis of a two week visit that he made to Britain in June 1971 when he stimulated great interest in scientists working in the field of electrochemistry.

Professor Levich has, however, been informed by Academician Frumkin that he cannot accept the offer from Oxford.

During the past five months Professor Levich has been expelled from the Scientific Council of the Institute of Electrochemistry of the Academy and from the editorial board of the Journal of Electrochemistry. He has also been removed from the Scientific Councils of the Mechanical Faculty of the university and of the Institute for Problems of Mechanics of the Academy. And he is no longer a member of the editorial board of the Journal of Theoretical Foundations of Chemical Engineering.

AIR POLLUTION

Britain Breathes Sweeter

BRITAIN'S air is undeniably getting cleaner. The first volume of the National Survey of Air Pollution (HMSO £3.50) published last week reveals that smoke emissions have fallen by almost 60 per cent since 1961 and that sulphur dioxide emissions have fallen by 30 per cent.

The most dramatic improvement has come in industrial smoke emissions. Since 1950 these have fallen from 1.11 million tonnes of smoke to 0.13 million tonnes, while domestic smoke output has only fallen by 0.67 million tonnes to 0.64 million tonnes a year. These improvements have been achieved in spite of a 9 per cent increase in population and a 29 per cent increase in energy consumption.

The chief causes of the decline in emissions are that industry is burning more oil than coal (industrial coal consumption has fallen 50 per cent since 1962) and more wives are working and thus less fuel is burnt at home; central heating has also made inroads into the smoke output. Nevertheless 85 per cent of the current smoke output comes from domestically burnt coal in open fires.

Concentrations of smoke are still appreciably worse in the north of England than the south—concentrations reached $88 \mu\text{g m}^{-3}$ in the north against $31 \mu\text{g m}^{-3}$ in the south east but the relationship between coal burnt and smoke emitted is not linear. Thus south Wales burns as much coal per head as the north of England, yet because the coal from its pits is relatively smokeless the towns in south Wales have a lower concentration of smoke than the towns in any other region.

The sulphur dioxide story is not quite so impressive. Since 1950 domestic output of SO_2 has fallen from 0.86 million

tonnes to 0.50 in 1970. Output by industry, however, has remained roughly the same, but output by power stations has climbed steadily to 2.64 million tonnes in 1970 from 0.95 million tonnes in 1950. Warren Springs Laboratory which is responsible for the survey claims this is still something of an achievement in that the total amount of SO_2 output has remained roughly constant at about 5.90 million tonnes since 1962 in spite of a population increase of 4.4 per cent and a 16 per cent leap in energy consumption. London's SO_2 levels are marginally higher than those in the north, although outside London the levels fall appreciably—only $79 \mu\text{g m}^{-3}$ in the south east compared to $140 \mu\text{g m}^{-3}$ in Yorkshire and Humberside. In spite of the higher levels the report suggests that legislation to control sulphur dioxide emission may not be necessary as the introduction of increasing quantities of low-sulphur oil and sulphur-free gas and

nuclear power is gradually reducing the sulphur dioxide emissions. Local measures may, however, be needed in large cities in the Midlands and the north, the report says, on the lines already adopted by the City of London which prohibits the use of fuel oil containing more than 1 per cent sulphur.

The report reveals that London has undergone the most dramatic changes in smoke patterns, with emission falling from about 170,000 tonnes in 1951 to about 17,000 tonnes in 1970. As a result the annual average smoke concentration has tumbled from $250 \mu\text{g m}^{-3}$ in 1954 to $45 \mu\text{g m}^{-3}$ in 1970.

The report is the first of a series of four summarizing the results of the 10 year survey of air pollution which began in 1960. The later volumes will deal with the regional pictures whereas this volume includes a detailed survey of the south east as well as an overall view of the country's air pollution problems.

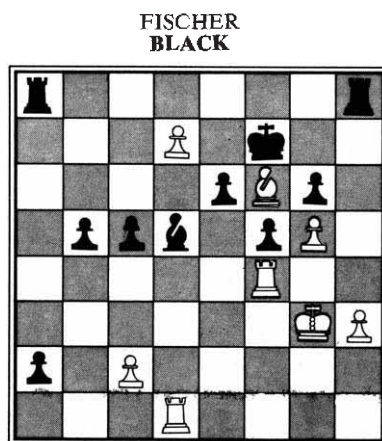
Fischer Moves On

THE twelfth game of the Spassky-Fischer match was a relatively quiet affair. The opening was a form of Queen's gambit declined which was favoured more by the masters of fifty years ago than it is by those of today. Spassky did well to thwart all Fischer's attempts to make headway and was never in any real danger of losing.

The thirteenth game was a bitter struggle and the longest one of the match so far. Spassky playing white against an Alekhine's defence was unwise to choose the variation which lost a pawn early on for only nebulous attacking prospects. Spassky fought hard, however, and at the cost of another pawn managed to reach an ending with rooks and bishops of opposite colour which allowed distinct drawn chances by the first adjournment.

The diagram shows the position in this game after white's 42nd move, the sealed move at the end of the first session. Fischer chooses a continuation which at first sight looks risky by allowing Spassky to penetrate with one of his rooks and necessitating the sacrifice of a bishop for a third pawn. Fischer's advanced pawns still give him the initiative, however, and Spassky tires in the defence and permits Fischer to win at the very last moment.

This loss must have sapped Spassky's mental resources severely just at the point when he desperately needed a recovery and the chances of a Fischer victory in the match as a whole must now be very strong.—J. P.



Position after White's 42nd move in the thirteenth match game

White: Spassky Black: Fischer Alekhine Defence

White	Black	White	Black
1 P-K4	N-KB3	38 B-B6	P-R6
2 P-K5	N-Q4	39 R-B4	P-R7
3 P-Q4	P-Q3	40 P-B4	BxP
4 N-KB3	P-KN3	41 P-Q7	B-Q4
5 B-QB4	N-N3	42 K-N3	R-R6 ch
6 B-N3	B-N2	43 P-B3	KR-R1
7 QN-Q2	O-O	44 R-KR4	P-K4
8 P-KR3	P-OR4	45 R-R7 ch	K-K3
9 P-QR4	PxP	46 R-K7 ch	K-Q3
10 PxP	N-R3	47 RxP	RxP ch
11 O-O	N-B4	48 K-B2	R-B7 ch
12 Q-K2	O-K1	49 K-K1	KxP
13 N-K4	N(N3)xP	50 R(K5)xB ch	K-B3
14 BxN	NxB	51 R-Q6 ch	K-N2
15 R-K1	N-N3	52 R-Q7 ch	K-R3
16 B-O2	P-R5	53 R(Q7)-Q2	RxR
17 B-N5	P-R3	54 KxR	P-N5
18 B-R4	B-B4	55 P-R4	K-N4
19 P-KN4	B-K3	56 P-R5	P-QB5
20 N-Q4	B-B5	57 R-QR1	PxP
21 Q-Q2	Q-Q2	58 P-N6	P-R5
22 QR-Q1	KR-K1	59 P-N7	P-R6
23 P-B4	B-Q4	60 B-K7	R-KN1
24 N-QB5	Q-B1	61 B-B8	P-R7
25 Q-B3	P-K3	62 K-B2	K-B3
26 K-R2	N-Q2	63 R-O1	P-N6 ch
27 N-Q3	P-QB4	64 K-B3	P-KR8=Q
28 N-N5	Q-B3	65 RxQ	K-Q4
29 N-O6	OxN	66 K-N7	P-B4
30 PxQ	BxQ	67 R-Q1 ch	K-K5
31 PxR	P-B3	68 R-QB1	K-Q6
32 P-N5	RPxP	69 R-Q1 ch	K-K7
33 PxP	P-B4	70 R-QB1	P-B6
34 B-N3	K-B2	71 B-B5	RxP
35 N-K5 ch	NxN	72 RxP	R-Q2
36 BxN	P-N4	73 R-K4 ch	K-B8
37 R-KB1	R-R1	74 B-Q4	K-B8
		Resigns	P-B7

NEW WORLD

US Physics Healthy but Financially Undernourished

by our Washington Correspondent

DURING the past few years, the National Academy of Sciences has set up a number of committees to inquire into the health of various branches of science in the United States. The committees have consisted almost exclusively of distinguished members of the discipline under investigation and so, not surprisingly, their reports have turned out to be remarkably similar to each other—they have been elegant pleas for more money, justified on the grounds that the discipline is intellectually appealing, that it holds great promise of exciting new discoveries, some of which may benefit society, and that US preeminence in the field is in danger because of lack of cash.

The latest in the line, a massive report on the health of physics in the United States, is no exception to the trend. A committee under the chairmanship of Dr D. Allan Bromley of Yale University has argued that budgetary stringencies that began during the late 1960s have seriously endangered the health of physics, caused manpower surpluses and threaten to relegate the US to a second-rank physics power (*Physics in Perspective*, available from the National Academy of Sciences, 2101 Constitution Ave NW, Washington, DC 20418). And this has come at a time when physicists are bursting with good ideas to exploit.

But, tempting as it may be to dismiss the physics report as simply a plea for more money from a committee stacked with vested interests—and that is undoubtedly how many will view it—it deserves much more serious attention. The fruit of some two and a half years of labour, the 1,000-page report is perhaps the most ambitious attempt yet to take stock of an entire field of science, and it is replete with information and analyses. It is also a genuine attempt to tackle the prickly task of determining priorities if funding in physics fails to grow at a rate at which all worthwhile ideas can be exploited.

The overriding message in the report is that physics in the United States is alive and well, but in need of a transfusion of new capital to heal some of the wounds caused by the levelling off in funding which started in 1967. As Dr Bromley puts it in his introduction to the report, “most striking among the findings of this survey are the overall power and vitality of American physics. . . . But this strength is in danger”.

In the 1950s and early 1960s, physics,

like other branches of science in the United States, experienced a period of burgeoning growth. Then suddenly in 1967, the budget levelled off and since that time it has stayed approximately constant in real terms, and perhaps even declined, so that in 1972 the federal physics budget stood at about \$450 million (the federal government provides about 85 per cent of the total US expenditure on physics). The sudden halt in the growth rate came at an unfortunate time, not only because it followed a period of rapid growth during which many new ideas had been generated and were awaiting funding, but also because the universities had zealously responded to the call for increased production of science PhDs, and had cranked up to peak output. A greatly increased number of PhD physicists were then dumped onto the employment market just at the time when budgets started to contract.

Consequently, for the past five years, US physics departments have been forced to take in their belts and unemployment among physicists has been steadily growing. But, even after this period of financial stringency, US physics is still in the forefront of international endeavour, so how credible is the committee's contention that “even with the most judicious use of existing resources, this nation cannot continue as a leading contributor to world physics without support greater than is now available”? Countries which devote less to science in general than the US does to physics alone will surely look askance at that statement.

The committee's argument is that during the period of financial stringency, the physics community has taken a variety of measures which have worked well on a temporary basis, but which have not laid a good base for future operations. Among the expedients which Dr Bromley cites are a drop in the hiring of young people, and a decline in updating instrumentation. “We have been living on our capital of new ideas, instrumentation and bright young minds”, he said at a press conference last week, and indicated that such policies may work well in the short term, but “pay no regard to the generation that comes next”. The holding operation over the past few years has, however, avoided wholesale dismantling of research groups, but the committee believes that unless the funding decline is reversed, such a fate is not far off.

But would it matter if the United

States lost the lead in some areas of physics by shutting off research funds to some groups and consolidating resources in others? Few other countries, after all, can afford the luxury of supporting every type of physics research, and they must make conscious decisions to put their eggs in a few baskets. The committee counters this suggestion by a variety of arguments, perhaps the most powerful of which is that to abandon whole areas of research would not only destroy the fruitful inter-relationships that now exist in American physics, but would also write off the considerable expenditure that has been invested in such areas. Moreover, the loss in human resources is one on which no dollar figure can be placed. “Not to use available human resources . . . is to waste resources, not to conserve them”, the report points out.

Nevertheless, unless there is a spectacular upturn in science funding in the United States during the next few years, painful priority decisions must be made, and some research programmes may have to go by the board. How the committee has tackled these questions is the nub of its report. The committee has presented a long discussion of how it set about determining priorities, and wound up with criteria based on intrinsic merit (“criteria internal to science”), extrinsic merit, which “relates to impact on technology and on the resolution of human problems” and structure, which “is concerned with impact on the national capability to do physics”. The criteria are very similar to those developed by Dr Alvin Weinberg, a member of the survey committee (*Minerva*, 1, 159; 1963).

The committee appointed panels of physicists from all the various subfields of physics, and asked them to apply the criteria to their fields to determine the consequences of four different levels of funding: an exploitation programme, designed to exploit all worthwhile opportunities in the field, a level programme designed to utilize a funding level held constant in the most effective fashion, an intermediate programme midway between these two levels, and a declining programme in which the budget level, after correcting for inflation, declines at 7.5 per cent a year.

What emerged from the panel considerations was that an annual growth rate of about 11 per cent would allow full exploitation of ideas, a rate that is clearly wishful thinking, but which nevertheless would not allow physics support to reach the level in 1977 which it would have reached if a modest 5 per

cent growth rate had been maintained since 1967. Declining budgets would result in whole areas of physics being abandoned, the committee found, and similarly static budgets would seriously undermine US capabilities because the holding operation described above would be made permanent, and insufficient regard could be paid to future generations of physicists. As for the intermediate funding level—"typically involving a 6.5 per cent growth rate", the report suggests—part II of the report, to be published later, outlines the effects on each subfield of physics.

The committee does not attempt to come up with a recommendation of what level of funding should be maintained during the 1970s, a decision which the report says "does not reflect unwillingness to face the difficulties inherent in any such attempt. Rather, it reflects the conclusion that it is impossible for any group such as the Physics Survey Committee to develop either adequately complete information or the insight to make such a detailed attempt meaningful." Nevertheless, the likely consequences of various funding levels on elementary particle physics and nuclear physics—two branches that are dominated by expensive new facilities, but which account for about half the total physics expenditure in the US—are useful guides.

In each of these fields, new large facilities are about to begin full operation—the Los Alamos Meson Facility (LAMPF) in nuclear physics and the National Accelerator Laboratory (NAL) in elementary particle physics. The committee report points out that financial stringencies in each of these two fields have caused other facilities to be shut down, and unless large increases for operating costs are provided very soon, even more painful decisions must be made. LAMPF, for example, requires \$7 million for operations in 1973, but only \$1.5 million has been provided. Similarly, NAL will require an extra \$20 million in 1973, but the entire budget for elementary particle physics has been increased by only \$10 million. The committee suggests that "if the additional funds are provided entirely at the expense of the operating budgets of the remaining facilities, the net effect on them will be drastic indeed. It is difficult to see how the ZGS and the Bevatron could survive; such a loss of two of the nation's four proton accelerator facilities would severely damage the national effort in elementary particle physics". The Administration's answer is to budget for an operating level in the NAL of 70 per cent capacity (see *Nature*, 236, 52; 1972), a situation which, of course, reduces the return on the investment in the machine.

As for physics manpower, the com-

mittee has done its own study, and comes up with some bleak conclusions. The dislocation that resulted from budgetary cutbacks just as the universities were producing PhDs at a peak rate is likely to continue, at least until the mid-1970s. Based on the number of graduate students at present in the PhD pipeline, the committee estimates that some 7,000 PhD physicists will be produced between 1970 and 1975, and that this could result in a surplus of between 2,300 and 4,200. Beyond 1975, however, if the economy improves, and if the downward trend in enrolments continues, "overproduction of PhDs may not be a problem", the report suggests.

To help alleviate the unemployment situation in the meantime, the committee recommends that departmental research groups should "replace a significant fraction of their graduate student complement with post-doctoral research associates". The committee also flies a kite by suggesting that "federal agencies should develop, for at least the immediate future, research funding mechanisms and appropriate criteria that would permit selected physics faculty members and colleges or smaller universities to engage in research without training graduate students".

Finally, the committee has some words to say about the federal government's mechanisms for supporting physics. Reiterated several times is the committee's belief that the strength of US physics owes much to the existence of a multiplicity of funding agencies, and the committee observes that "although we must view the diminishing funding levels of the past few years with the greatest concern, we cannot seriously fault the mechanism by which they have been allocated". The committee, in fact, argues that mission oriented agencies should strengthen their research programmes, and agencies such as the departments of Transportation and HEW should support more physics. On the other hand, however, the committee believes that the National Science Foundation should have its budget for basic science increased, so that it can act better as a flywheel to damp down oscillations in the budgets of other mission oriented agencies, and to help it to carry out its mission of ensuring the health of basic science in the US.

ASTRONOMY

Fourth Time Lucky?

by our Washington Correspondent
OAO-C, the fourth and most complex satellite in NASA's series of orbiting astronomical observatories, is scheduled for launch next week. The satellite, which will carry experimental packages from Princeton University and Uni-

versity College, London, is an improved version of OAO-B, which failed to go into orbit in November 1970. So far, only one satellite in the series, OAO-2, which was launched in 1968, has been an unqualified success—the first OAO failed after three days in orbit because of a fault in the power system.

The chief experiment aboard OAO-C is the 82-centimetre Princeton telescope which will be able to view stars down to sixth magnitude in ultra-violet light. The telescope will be used to study interstellar absorption of hydrogen, oxygen, carbon, silicon and other elements in interstellar gas and to investigate ultra violet radiation between 930 and 3,000 Ångströms emitted from young hot stars.

The London University experiment, which is being directed by Professor R. L. F. Boyd, consists of three small X-ray telescopes. It will complement the work of NASA's Uhuru satellite by searching for new X-ray sources and mapping more precisely other known sources.

The satellite will be renamed Copernicus if launch is successful, to commemorate the 500th anniversary of the Polish astronomer's birth.

Short Note

Budgets cleared, face veto

CONGRESS has finally agreed upon the budgets for the National Science Foundation, NASA and the National Institutes of Health for fiscal year 1973 (which started on July 1). Final appropriations for the National Science Foundation totalled \$626 million (including \$7 million in foreign currency), \$28.4 million less than the administration requested. NASA has been voted \$3,310 million, nearly \$100 million less than the Administration requested. The National Institutes of Health, however, have fared much better—Congress had added some \$213 million to the budget request, bringing the appropriations for the research institutes to \$1,794 million compared with \$1,476 million voted last year. The budgets now go to President Nixon for signature, but it seems very likely that he will veto the funds appropriated for NIH since they are contained in a bill which adds more than \$1,700 million to the administration's budget request for the departments of HEW and Labor. Nixon has recently made several public statements about fiscal responsibility, and Elliott Richardson, Secretary of HEW, said after passage of the appropriations bill that a Presidential veto is likely. The amount added to the HEW bill is, however, almost identical to the cut made by the Senate in the Military appropriations bill.

NEWS AND VIEWS

How does Interferon Act?

JUST as the clinician prefers to use Occam's razor (or a single diagnosis) to explain the many symptoms and signs in a given patient, so the biochemist would prefer to identify a single mechanism of action for all the effects of a biologically active material. Yet evidence has been presented indicating both translational (inhibition of protein synthesis) and transcriptional (inhibition of messenger RNA synthesis) levels of action for the antiviral activity of interferon.

On page 385 of this issue of *Nature*, Metz and Esteban describe findings that support a primary action of interferon at the translational level. About 30 minutes after vaccinia infection of L cells they observed inhibition of synthesis of virus proteins without any inhibition of viral RNA synthesis. In fact, viral RNA synthesis as measured by the incorporation of radioactive uridine increased during interferon treatment (without any change in the UTP pool size). The translational effect can be demonstrated in terms of either net viral protein synthesis in infected cells or in incorporation of ³⁵S-labelled methionine into virus associated peptides (examined by electrophoresis of cell extracts). During the second group of experiments no changes were observed in methionine uptake or intracellular pool size, suggesting that the effect of interferon is a consequence of a real decrease in synthesis rate. This effect on translation in the absence of a transcription effect is also found by Metz and Esteban in the action of interferon against vaccinia in chick cells and was observed with several interferon preparations, including low doses of highly purified material.

The authors have also participated in other work, which is published in the August 1972 issue of *FEBS Letters*, which indicates that interferon treatment has a significant effect on cell free synthesis of viral proteins. Here, Friedman, Esteban, Metz, Tovell, Kerr and Williamson describe a striking and selective inhibition of viral protein synthesis using viral RNA and ribosomes and cell sap from infected cells treated with interferon. Ribosomes from these cells failed to translate encephalomyocarditis virus RNA but translated both globin messenger RNA and poly (U) at normal rates. Apparently this effect of interferon on ribosomes can best be demonstrated if the cells treated with interferon are also infected, as though infection actually intensifies the intracellular antiviral state produced by interferon. Again small amounts of purified interferon work well and various physical or chemical procedures which destroy the antiviral effect of interferon also prevent this effect, as does the use of interferon resistant (Krebs) cells as a source of ribosomes and cell sap for the cell free synthesis system.

The background for this work is typical of any field where there is an intense interest in defining the mechanism at the molecular level of a biologically active material. There are shifts in allegiance to various hypotheses as new findings occur; for example, early studies with vaccinia, mengovirus and Semliki Forest virus all indicated that interferon acts at a translation

level. In fact, Marcus and Salb published evidence that in a cell free system utilizing Sindbis messenger RNA, ribosomes from cells treated with interferon did not behave like ribosomes from untreated cells. Unfortunately Kerr and other workers have had difficulty reproducing or extending these observations and no subsequent work along these lines has appeared from Marcus's laboratory. But recently Marcus (working with vesicular stomatitis virus, VSV) and Colby (working with vaccinia) and their coworkers have produced evidence suggesting that interferon will act in cells treated with cycloheximide-actinomycin to inhibit viral RNA synthesis directed by the transcriptase associated with the infecting virion. Furthermore, studies of the action of interferon against SV40 by Oxman and Levine have been interpreted in terms of a transcriptional level of action for interferon.

Whether Metz and Esteban and Colby *et al.*, with their apparently conflicting findings, are studying the same vaccinia RNA species is impossible to say at present as both have used different methods of characterizing them. The former group relied on the size of the species, and early, rapid synthesis in virus infected cells that had been treated with actinomycin, to indicate a viral origin. On the other hand, Colby *et al.* demonstrated, as did Marcus and associates and Oxman and Levine, that the RNA which they found to decrease on treatment with interferon could be annealed to purified viral DNA. The effect of interferon on VSV transcriptase has also been confirmed and extended by Huang and her colleagues. All these studies, however, depend on the precise action of the metabolic antagonists for the conclusion that interferon inhibits viral biosynthesis solely through a transcriptional action. Even a little residual protein synthesis might allow a translational action to produce transcriptional effects. Moreover, secondary effects of these inhibitors in infected cells treated with interferon, and/or impurities in the crude interferon preparation used, might be responsible for the transcriptional inhibition found.

The next critical step in establishing a transcriptional action of interferon is to demonstrate that cells treated with interferon or extracts of interferon will inhibit RNA synthesis mediated by transcriptase in a cell free system utilizing highly purified virions. Unfortunately, in spite of some serious efforts, such findings have not been forthcoming although purified virion transcriptase activity has been easily demonstrated in many laboratories. Such experiments would, first of all, avoid the limitations in interpretation associated with studies using metabolic antagonists. Second, further studies to determine a precise molecular level of mechanism of action by using purified macromolecular components would be possible, and perhaps even studies at a polynucleotide sequence level to examine why the effect of interferon is selective in its inhibition of viral rather than host messages could be contemplated. This would contrast with the kinds of investigation which have been possible so far—that is, chiefly descriptive attempts to pin down the point at which interferon acts in the viral replicative cycle.

The *in vitro* work of Friedman *et al.* may also allow

definition of the molecular level of action of interferon and perhaps even the nature of the elusive protein thought to mediate its action in cells. The exact change in the ribosomes of cells treated with interferon—more precisely in the RNA or protein components of the ribosome—might be demonstrable. This could be similar to the minor but critical change which Nomura and his colleagues found in ribosomes from bacterial cells treated with colicin (that is, a single break in one of the ribosomal RNA components) which they think underlies the mechanism of action of this similarly potent protein.

At present, there are clearly two possible sites of action for interferon—virus translation and transcription—and the action could even take place at two different sites, one or the other of which might prevail in a particular infection. Keen interest in this question will continue, and, given some time and progress in understanding viral replication at the molecular level, there will undoubtedly be clarification of the apparently conflicting data. A final point to be made is that this substance and its site of action may have an even more fundamental significance for students of animal cell function. Viral biochemistry has long been used as a model for and probe of normal cellular function. As both Gresser and others have pointed out, interferon acts on intracellular parasites more complicated than viruses (which contain their own ribosomes) and also seems to inhibit division of tumour or certain other rapidly dividing cells. It may, therefore, play a critical regulatory part in the control of cell division or the expression of polynucleotide functions in normal cells.—T. C. M.

On Stringent Response

IN 1952 Sands and Roberts (*J. Bact.*, **63**, 505) showed that when a bacterial strain was deprived of a certain required amino-acid, not only did protein synthesis stop but RNA synthesis was also substantially reduced. This observation was the first suggestion that the regulation of RNA synthesis in bacteria might be closely coupled to protein synthesis. The characterization of this control system proceeded slowly and sometimes painfully until in 1961 Stent and Brenner (*Proc. US Nat. Acad. Sci.*, **47**, 2005) demonstrated that mutation at a single genetic locus, the RC or *rel* locus, altered the control mechanism in such a way that RNA synthesis was no longer reduced when a required amino-acid was withdrawn. These mutants, which were recessive to the parental allele, were said to possess relaxed control of RNA synthesis, whereas the parent strains were said to exercise stringent control. Meanwhile on the biochemical front it was established that a critical step in effecting the stringent response was a cell's failure to aminoacylate a transfer RNA species. Furthermore, most evidence suggested that at least in *Escherichia coli* the synthesis of stable rRNA and tRNA species was preferentially restricted relative to mRNA species during the stringent response. The stringent response is thus a regulatory mechanism in which the synthesis of a specific class of RNA is preferentially controlled.

What then is the molecular mechanism of stringent control? A key observation was reported in 1969 by Cashel and Gallant (*Nature*, **221**, 830), who observed

that when a stringent cell was functionally starved of an amino-acid two unusual "magic spots" rapidly appeared on the chromatogram used to analyse the nucleotide components of the bacterial cell. These magic spots, otherwise christened MSI and MSII, were subsequently identified respectively as a guanosine tetraphosphate, ppGpp, and a guanosine pentaphosphate, probably pppGpp. Knowing the physiological conditions that promoted the appearance of these compounds, and also that they rapidly disappeared in the presence of chloramphenicol, an inhibitor of protein synthesis, Cashel and Gallant proposed that the MS nucleotides were synthesized during an idling step in protein synthesis and also that one of the protein synthesis factors was required for their synthesis. They further suggested that the MS nucleotides, in particular ppGpp, functioned as inhibitors of low molecular weight, affecting preferentially the synthesis of stable RNA.

Since the announcement of the existence of the MS nucleotides much effort has been expended in attempting to determine their function and the mechanism of their synthesis. In a timely contribution to this issue of *Nature* (page 381) Haseltine, Block, Gilbert and Weber present a series of strikingly straightforward experiments which confirm and extend many of the hypotheses of Cashel and Gallant concerning the synthesis of the MS nucleotides. Following the classic biochemical procedures of identifying an enzymatic reaction in a crude extract and then purifying the necessary components of the reaction the Harvard group has been able to show that the MS nucleotides are synthesized on the ribosome. This synthesis requires a factor that is washed off ribosomes by high concentrations of salt, and also the G translocation factor. Consequently the synthesis is suppressed by antibiotic inhibitors of G factor. GDP acts as the precursor for MSI synthesis and GTP as the precursor for MSII synthesis; perhaps surprisingly ATP is also required and the authors speculate that ATP may be implicated in normal protein synthesis.

Of particular interest is the factor in the high salt wash. This necessary component is, as predicted, found only associated with ribosomes isolated from stringent cells, being absent from ribosomes isolated from relaxed cells. Haseltine *et al.* suggest that the factor may sense when the aminoacyl tRNA site on the ribosome is vacant. Such a vacancy would of course occur when the cell is starved of an amino-acid. On recognition of the vacancy the net synthesis of the MS nucleotides would be triggered in an idling translocation reaction. This scheme leaves open the possibility that MS nucleotides may be synthesized as normal transient intermediates in protein biosynthesis.

Nevertheless the story of the synthesis of MS nucleotides is far from closed. Although relaxed strains do not accumulate these compounds as a response to amino-acid starvation, they do accumulate these compounds in response to other changes in cell conditions such as carbon source downshift or a high salt shock. Whether this synthesis is a consequence of the ribosomal mechanism responding to a different signal or of a completely different synthetic pathway remains to be established. Another puzzle, over which a discreet silence is maintained, is the mode of breakdown of ppGpp in the cell.

The synthesis of MS nucleotides on an idling ribosome starkly poses the question of their function. Do

they perform a regulatory role in the cell or is their synthesis merely a metabolic safety valve? The most compelling evidence that they are involved in regulation comes not from the stringent response—which may be regarded simply as an emergency shutdown of many cellular functions—but from the observation of Lazzarini *et al.* (*J. Biol. Chem.*, **246**, 4381; 1971) that the concentration of ppGpp in cells growing normally varies inversely with the growth rate, and coincidentally with the rate of stable RNA accumulation.

The crucial problem thus centres on the nature of the target of ppGpp in its regulatory role in the context of RNA synthesis. Apart from various enzymes involved in nucleotide metabolism ppGpp is known to interact with and inhibit one component of the transcription machinery, the RNA polymerase itself, and also two components of the protein synthesis machinery, the initiation factor IF2, and the elongation factor Tu. In the latter cases ppGpp seems to act quantitatively as an analogue of GDP whereas in the former case ppGpp is a far stronger inhibitor than GDP.

Does the interaction of ppGpp with any of these proteins directly regulate the synthesis of stable RNA? Haseltine (*Nature*, **285**, 329; 1972) has shown that the proportion of rRNA synthesized by highly purified RNA polymerase *in vitro* is not significantly affected by ppGpp. The effect, if any, of IF2 on the specificity of transcription is unknown. The elegant equation of the putative rRNA synthesis control factor, psi, with the elongation factor Ts Tu (Blumenthal, Landers and Weber, *Proc. US Nat. Acad. Sci.*, **69**, 1313; 1972) points, however, to a mode of positive control of stable RNA synthesis mediated by a component of the protein synthesis machinery. The activity of the control element would be negatively regulated by the concentration of ppGpp relative to that of GTP. If Tu should be confirmed as a regulatory target of ppGpp—and a *sine qua non* of confirmation is minimally a demonstrable functional association of RNA polymerase and Tu—a molecular mechanism for the coupling of stable RNA production to protein synthesis would have been formulated from the concerted labours of the past twenty years.—A. A. T.

DEMOGRAPHY

Change in Ireland

THE past decade has seen a rapid reduction in the Irish Republic in the age of marriage which, according to Brendan M. Walsh (*Demography*, **9**, 187; 1972), means that Ireland "will before long cease to be remarkable by European standards in regard to nuptiality". For most of the past century, Ireland has been remarkable not merely for its late age of marriage but also for the proportions of men and women remaining unmarried, in which circumstances it is surprising that Walsh says that the only reliable information on age of marriage in Ireland before 1957 was a special inquiry into marriages of less than one year's duration included in the 1946 census. That inquiry showed that in the Republic of Ireland as a whole, the median age of marriage was 27.0 years for women and 31.8 years for men (with remarriages included). By 1957, the median age at first marriage was 25.9 for women and 29.4 for men, representing a small decrease since 1946 when remarriages were included.

In the remainder of the 1950s, the median ages of marriage remained the same, but in the 1960s there seems to have been a quite rapid decrease of median marriage age, which amounted in 1969 to 23.8 years for women and 26.0 years for men. Walsh points out that the contrast between the 1950s and the 1960s corresponds with the difference in the pace of economic growth of the two periods, which amounted to 30 per cent (in real terms) per head between 1946 and 1957 and to 46 per cent

between 1957 and 1968. During the whole period, the reduction of the age of first marriage of men has been greater than that of women, with the result that the difference between the median ages of men and women at first marriage has decreased from 4.8 years in 1946 to 2.2 years in 1967.

The well known difference between the marriage patterns in towns and in the countryside persists, but not all the change in the pattern of nuptiality in Ireland since 1946 can be accounted for by the displacement of farming people to the towns. In 1946, the median age of marriage for women was 25.8 years in the towns and 28.0 years in the country (the corresponding figures for men are 29.2 years in towns and 33.6 in rural areas). From Walsh's analysis of marriage patterns in terms of occupation, it is apparent that even among the farmers, who are traditionally the last to marry, the median age of marriage has decreased from 36.1 years in 1946 to 31.7 years in 1969. Among farm labourers, the median age at marriage had decreased to 27.4 years, substantially the same as the median age at marriage of professional men in Ireland. Farm labourers remain conspicuous, however, because of the high proportion remaining unmarried—in 1966, sixty per cent of farm labourers over the age of 14 were unmarried.

Walsh points out that the frequency distribution of age at marriage is highly skewed, especially for women. Over the years, however, there has been a tendency for the age at marriage to conform more closely with the mode—in other words, smaller proportions of men

Revealing C-type Viruses

ACCORDING to the doctrine of Huebner and Todaro all cells inherit genes capable of inducing a transformation to malignancy, so-called oncogenes, and also genes capable of specifying a C-type virus, so-called virogenes. When both oncogenes and virogenes are expressed the result is a malignant cell releasing RNA tumour viruses, whereas when oncogenes alone are expressed the cell is transformed but fails to release virus. Any cell infected and transformed by an exogenous RNA tumour virus should, according to this hypothesis, have two sets of oncogenes and virogenes. Experiments which can be interpreted in this way are reported in the next issue of *Nature New Biology* (August 23) by Klement and six of his colleagues.

Klement *et al.* exposed a clone of rat cells of the XC cell line to 5-bromodeoxyuridine (BrUdR) and as a result induced the production of an RNA C-type virus which contains reverse transcriptase. During its ten-year history the XC cell

line, originally isolated by Svoboda, who raised a tumour in a newborn Wistar rat with the Prague strain of Rous (avian) sarcoma virus, has been repeatedly passaged *in vivo* and *in vitro*. XC cells contain the group specific antigen of the avian tumour viruses, and the Rous genome can be rescued by fusing these rat cells with chicken cells. On their own the XC cells do not produce Rous virus.

Several tests show, however, that the virus induced by Klement *et al.* from their clone with BrUdR is not the Prague Rous sarcoma virus. Rather it seems to be a rat virus, for it cross-reacts with antisera to the rat species specific gs-1 antigen; the virus does not, however, transform or cause any detectable cytopathic effect in the rat cells that have so far been tested. These XC cells, as Klement *et al.* suggest from these findings, may well contain two sets of genes capable of specifying a C-type RNA virus, exogenous avian and endogenous rat.

and women have been postponing marriage to an advanced age. One feature of the change has been a tendency for the inequality of age of marriage to decrease, but Walsh points out that the proportion of women aged 25 or more who marry men younger than themselves has actually increased.

On the question of whether the changing pattern of nuptial age may be explained by an increased supply of younger marriageable men, Walsh says that the increased proportion of women marrying men aged 20–24 has coincided with an increase in the proportion of such men in the population, but that the increased supply of these men cannot account for all the change and that changes of "taste" and in particular the current unwillingness of women to marry men much older than themselves is an important part of the explanation.

Although Walsh's article does not explicitly deal with the effects of these changes on fertility, he says that the trend towards earlier marriage in the Republic of Ireland is part of a general tendency towards increased nuptiality and lower fertility which, he says, coincides with the growth of the use of contraceptive pills in Ireland since 1960.

PROTEINS

Hunting Heterogeneity

from our Molecular Biology Correspondent
THE isoelectric focusing technique, especially in polyacrylamide gels, is a two-edged sword. What pleasure there is in contemplation of the exquisite resolution is generally soured by the implications of the results for the homogeneity of one's protein preparations; too much resolution can be just as hard to live with as too little. It is at all events now clear that micro-heterogeneity is a phenomenon of wide prevalence, whose causes and physiological consequences are by no means understood. It seems that in some cases the components may represent alternative stable conformational sub-states, which may or may not be stabilized by corresponding disulphide pairings. In others the components are the possible oligomeric combinations of different subunits (the lactate dehydrogenases being an archetype).

In glycoproteins non-uniform distributions of saccharide units between different molecules have been found, and in some systems one encounters varying degrees of enzymatic phosphorylation, methylation or acetylation in a few residues. If none of these applies, and the imagination fails, there always remains the possibility of proteolytic damage, most probably as an artefact of the preparation, and of partial deamination of asparagine and glutamine residues. This last has at

times been mooted in vague terms, but since the reaction *in vitro* requires a highly alkaline pH, and no deaminases of the required specificity are known to exist, there has been little justification in invoking it. This has all now been changed by an admirably clear-cut series of experiments by Midelfort and Mehler (*Proc. US Nat. Acad. Sci.*, **69**, 1816; 1972).

The protein in question is aldolase, an enzyme with a chequered history. Contrary to past assertions, it now seems clear that the enzyme is a tetramer, which, in spite of the five components revealed by isoelectric focusing, contains two almost indistinguishable types of subunit, α and β . Indeed in a substantially complete comparison of the sequences in terms of peptide maps, only one substitution has been established. This occurs at the fourth position from the C-terminus, where there is an asparagine in the α , and an aspartic acid in the β , subunit. Midelfort and Mehler therefore considered the possibility that aldolase is in fact synthesized as a single homogeneous species, which undergoes specific deamination in one position during its lifetime. In such a case the order of the isoelectric points of the five isozymes, α_1 , $\alpha_2\beta$, $\alpha_2\beta_2$, $\alpha\beta_3$, and β_4 , would also be the order of their age.

Accordingly aldolase was prepared from the muscles of rabbits, which had been injected at various times with a radioactive label. The labelled residue was isoleucine, the C-terminus, which occurs in the same chymotryptic peptide as the single substitution. The results showed that the label appeared predominantly in the α chain at short times, and later progressively entered

the β chain. That this might be a consequence of faster synthesis (by a factor of 20 or so) of the α chain can be ruled out, for the 1:1 balance of α and β chains is maintained in the isozyme distribution. Furthermore, in isoelectric focusing, the radioactivity after a pulse label does not follow the concentration of protein (or of enzymatic activity across the isozyme distribution). The α_1 isozyme is strongly labelled, the others progressively less so, and the β_4 not at all.

Whether the deamination is enzymatic is not yet clear, but this certainly seems the easiest explanation. Some interesting consequences follow from the findings, one of which is that subunit exchange is immeasurably slow compared with the rate of metabolic turnover and deamination. Second, the results permit a simple estimate of the half-life of the aldolase molecule in the animal. One can solve the rate equations for the rates of synthesis and degradation, assuming the α and β chains to be degraded indistinguishably, with the result (allowing for an error due to reutilization of the label) that the half-time of survival is some eight days. The method which Midelfort and Mehler have applied to this work is perfectly general and will allow other isozyme systems to be analysed for differences in amide content.

An example of proteolytically generated heterogeneity is considered by Easterby and Rosemeyer (*Europ. J. Biochem.*, **28**, 241; 1972). If yeast hexokinase is prepared in the presence of serine protease inhibitors, two separable forms are electrophoretically resolved, and two others derived from these are eliminated. The molecules are

Stable RNA Breakdown in *E. coli* Mutant

WHEN bacteria are starved, their messenger RNA is rapidly degraded but their transfer RNA and ribosomes are degraded only very slowly. The selective advantage of the stability of these latter components is obvious, but at present there is little indication of how it is achieved. The properties of a new mutant strain of *Escherichia coli* described in *Nature New Biology* next week (August 23) by Ohnishi and Schlessinger show, however, that the turnover of stable RNAs is normally strictly regulated to a very low level.

The mutant strain V64S was selected after nitrosoguanidine mutagenesis and has a most unusual phenotype. Although the cells are not temperature sensitive when they are cultured at 42° C in the presence of inhibitors of transcription, either rifampicin or actinomycin D, both ribosomal and transfer RNAs are essentially totally degraded once all the messenger RNA has been broken down; DNA is not degraded.

This degradation of stable RNAs in the absence of transcription can, however, be prevented by adding inhibitors of protein synthesis which keep polysomes intact by freezing ribosomes on the messengers they happen to be translating.

The rate of degradation of messenger RNA in the mutant strain is the same as that in the parental strain, whereas the rate of degradation of the stable RNAs in the mutant is at least three or four times greater than in the parental strain. This indicates, of course, that the lesion in V64S is specific to some part of the system which normally regulates the turnover of stable RNAs, and even in the mutant the breakdown of stable RNA follows rules; it does not, for example, begin until the messenger RNA, and therefore the polysomes, have been degraded. Perhaps when the biochemistry of the lesion in this mutant strain is elucidated some light will be shed on the regulatory mechanism that ensures that stable RNAs are stable.

dimers of two apparently identical chains, each of molecular weight about 54,000. The damaged molecules are enzymatically active, but have an altered dissociating tendency. Dissociation of native hexokinase yielded on reassociation a new set of electrophoretic components, which, it is suggested, differ conformationally.

Kenney *et al.* (*ibid.*, 253) have been at pains to exclude proteolysis as the origin of isozymes in mitochondrial lipoyl dehydrogenase. In bovine and porcine heart preparations they find similar patterns of six major and two minor catalytically active species. Now the lipoyl dehydrogenase occurs both free and in 2-oxo-acid dehydrogenase multi-enzyme complexes. Kenney *et al.* have isolated these complexes separately, and have compared the isozyme composition of the lipoyl dehydrogenase from 2-oxoglutarate dehydrogenase and from pyruvate dehydrogenase. Essentially three of the major isozymes turn up in the one complex, and the other three in the other, in agreement with one set of earlier results. The free lipoyl dehydrogenase looks like the preparation from the pyruvate dehydrogenase complex, and is inferred to derive from this source. The basis of the charge differences within this collection of species can only be guessed at, and conformational substates seem as good a guess as any.

Enzymologists will be delighted to see (Bishop, Everse and Kaplan, *Proc. US Nat. Acad. Sci.*, **69**, 1761; 1972) that stopped flow kinetics are to be pressed into the service of clinical medicine. Heart and liver conditions are known to be accompanied often by changes in lactate dehydrogenase isozyme distributions, and these can be assayed in terms of kinetics of inhibition, as NADH is oxidized. It is true that they can more cheaply be assayed by electrophoresis, but this, as Bishop *et al.* point out, takes hours whereas their method takes seconds (leaving aside, of course, some hours to clean the machine in preparation for the next patient).

PHOSPHOLIPIDS

Gram-positive Charges

from our Membrane Correspondent

It is becoming clear that one of the ways in which bacteria accommodate themselves to otherwise unfavourable changes in their environment is by changing the phospholipid composition of their plasma membranes. In this way the cell is able to erect a barrier to the influx of undesirable ions or molecules. This kind of behaviour is illustrated in a report by Haest, de Gier, op den Kamp, Bartels and van Deenen (*Biochem. Biophys. Acta*, **255**, 720; 1972), who have studied the phospholipid composi-

tion of the membrane of *Staphylococcus aureus* and the way in which the membrane permeability of this Gram-positive bacterium responds to a lowering of the pH of its environment.

Two of the principal phospholipid components of this bacterial membrane are phosphatidylglycerol (PG), which is negatively charged, and lysylphosphatidylglycerol (LPG), which is the lysine ester of PG and therefore somewhat unusual in being a positively charged phospholipid. When the bacteria are grown or incubated at pH 7, the ratio of LPG to PG in the membrane is less than one, giving the membrane a net negative charge, whereas at pH 5 this ratio becomes considerably greater than unity so that the membrane acquires a net positive charge.

In order to assess the influence of these phospholipids on the membrane permeability, Haest *et al.* investigated the permeability properties of liposomes made from purified PG or LPG. (Liposomes are multilamellar vesicles of lipid bilayers and are a popular model system for studying the lipid barrier relevant to membrane permeability.) The LPG

liposomes proved to have a higher permeability to non-electrolytes such as erythritol and a lower permeability to Rb^+ than the PG liposomes. It was also found that valinomycin was able to increase the Rb^+ permeability only in the case of the PG liposomes. Haest *et al.* then studied the permeability properties of *S. aureus* cells grown or incubated at different pH values and found that the permeabilities behaved in the manner anticipated from the liposome experiments; the cells with a high PG/LPG ratio had lower non-electrolyte permeability, higher Rb^+ permeability and showed a much greater effect of valinomycin than cells with a high LPG/PG ratio.

The effect of LPG in increasing the non-electrolyte permeability is explained by the finding, from monolayer experiments, that LPG has a higher area per molecule than PG, and this implies that in bilayers containing large amounts of LPG the lipid molecules are somewhat loosely packed. In spite of this looser packing, the effect of LPG in reducing the cation permeability is evidently attributable to the overriding influence

More Experimentation in Petrology

ONE of the more important objectives of metamorphic and igneous petrologists is to estimate the final pressure (P) and temperature (T) regime of a particular group of rocks. The obvious method is to determine experimentally the PT field where the original phase (mineral) assemblage of the rock remains essentially unchanged; this kind of experimentation has been going on since the 1890s. During the 1950s there was a dramatic increase in the number of scientists working on experimental petrology and many advances in both technology and techniques have been made since then. Equipment is now available for subjecting samples to pressures and temperatures of up to 50 kbar and 1,500° C simultaneously, and these values are known to better than ± 2 kbar and $\pm 15^\circ$ C respectively. Very few rocks now on the Earth's surface have come from depths where the conditions are any more extreme than this. The attainment of equilibrium in experiments has been recognized as an important problem and a large part of any study will be directed towards proving that one phase assemblage is more stable than another, and has not just grown because of fast nucleation or persisted because of slow kinetics.

A good example of one type of study being done by experimental petrologists is presented by Vernon and Green in the next issue of *Nature Physical Science* (August 21). They have observed in a high grade metamorphic rock suite from central Australia the mineral cordierite associated with an inter-

growth of kyanite, quartz and gedrite, and have interpreted the intergrowth as a hydrated decomposition of the cordierite. The breakdown products and cordierite were separated in this experiment from the other minerals of the rock and from each other and then mixed in equal parts. The mixture was sealed with water in silver/palladium capsules and exposed to several combinations of high pressure and high temperature in an apparatus of the piston/cylinder type.

At the end of an experiment lasting 6 to 8 h the univariant reaction usually had not gone to completion but the direction of the reaction was known if the relative proportions of cordierite and intergrowth had changed. In this way the univariant line on a PT diagram separating the area in which cordierite is more stable from the area in which the assemblage, kyanite, quartz and gedrite is more stable has been bracketed. The line was found to be approximately parallel to the temperature axis at about 10.8 kbar, so it can be deduced that the host rock had been subjected to about this pressure of water vapour.

These and similar experimentally obtained results are strictly only pertinent to the assemblage actually used in the experiments, but in general the results may be used as an indication of the pressure and temperature of the same phase assemblage, although of somewhat different composition, from a different rock if allowance is made for the variation in chemical composition.

of the positive charge of the membrane. Thus it seems likely that the positive charge attributable to the increase in the relative amount of LPG in the membranes of cells grown at low pH plays a part in inhibiting the entry of H^+ ions into the cell. It is not clear, however, what advantage accrues to the cell from the concomitant increase in non-electrolyte permeability.

DEVELOPMENTAL BIOLOGY

Cell Cycles

from a Correspondent

THE cell cycle in development and cell differentiation was the subject of the twenty-fourth meeting of the British Society for Developmental Biology at the University of Bristol on July 25-27. Professor J. Mitchison (University of Edinburgh) said in his opening address that the cell cycle, in showing morphogenesis and structural and chemical differentiation, mimics many of the processes that determine the development of higher organisms. Dr G. Steel (Institute for Cancer Research) then critically reviewed the methods used for determining the intermitotic period, and warned of the difficulties inherent in analyses of the cell cycle in complex developing systems.

In a group of papers on unicellular and acellular organisms, Dr M. Ord (University of Southampton) described how he has combined *Amoeba* nuclei and cytoplasm from different stages of the cell cycle, and Dr D. Ammermann (University of Tübingen) discussed the cell cycle and differentiation in micro-nuclei and macronuclei of the ciliate, *Stylonychia*. Dr P. John (Queen's University, Belfast) reviewed the work of the Belfast group on *Chlorella*, stressing the pattern of synthesis of several enzymes and the formation of mitochondria and cell wall material in relation to the cell cycle as a whole. The advantages of working with a plasmodial slime mould, in which large numbers of nuclei can achieve a high degree of natural synchrony, were described by Dr W. Grant (University of Leicester).

The higher plants were also well represented in the symposium. Dr M. Bennett (Plant Breeding Institute, Cambridge) stressed the importance of nucleotypic control and described how the mass of DNA in the nucleus is a significant factor in determining the duration of meiosis. Dr P. Barlow (ARC Developmental Botany Unit, Cambridge) was concerned with the factors which determine the pattern of mitosis in root meristems, including the relation between the cap and the cells of the quiescent centre. Dr R. Lyndon (University of Edinburgh) discussed the

relationship between changes in the lengths of cell cycle phases and morphogenesis in the shoot apex, and Dr M. Yeoman (University of Edinburgh) described changes in enzymatic activities during the cell cycle in Jerusalem artichoke cells *in vitro*.

A further group of contributions dealt with the cell cycle during early development. Professor G. Giudice (University of Palermo) discussed the significance of the slow maturation of ribosomal RNA and the synthesis of histones during sea urchin oogenesis, in relation to the modified cell cycle which is characteristic of the early stages of development of many embryos. An account of the beautifully regulated chronology of cell division during the early development of molluscs was given by Dr J. van den Biggelaar (Utrecht), who described how the duration of the cycle relates not only to the subsequent fate of the cells but also to their previous history.

Dr L. Hamilton (Middlesex Hospital, London) demonstrated how the natural synchrony of the initial cleavage stages of development can be used for analysing the sensitivity of the various parts of the cell cycle to irradiation. Dr P. Chibon (University of Grenoble) showed that, whereas the lengths of the S, G₂ and M phases in the larval tissues of *Pleurodeles* shorten as the environmental temperature increases, the length of G₁ increases. Dr G. Rudkin (University of Nijmegen) discussed the

curtailed cell cycles of polytene cells of dipteran insects, in which chromosomal, nuclear and cell division are bypassed, leading to endoreduplication. Dr C. Graham (University of Oxford) said that the cell cycle is long during the early stages of cleavage in mammals, but shortens as cleavage proceeds while DNA accumulates by polyploidization in the trophoblast. Dr M. Snow (University of Edinburgh) indicated that the cells of the inner cell mass are particularly susceptible to radiation damage (including damage by ³H-thymidine) at the point in cleavage where the cell cycle is shortening.

The final session dealt largely with the control of cell proliferation by extrinsic factors. Dr P. Harrison (Beatson Institute, Glasgow) showed that erythropoietin induces both proliferation in proerythroblasts and an increased rate of haemoglobinization in foetal liver cells *in vitro*, and Dr R. Cole (University of Sussex) discussed genetic defects which upset the regulation of red cell formation in foetal mice. Dr D. Hardy (University of Birmingham) reviewed the mitotic activation of lymphocytes. He emphasized that there is not enough experimental evidence to support the idea that the process is the consequence of the direct action of stimulants, such as PHA, on the genome, evoking the action of new genes; it was far simpler to assume a rather less specific action at the cytoplasmic level.

Active Fragments from Growth Hormone

THERE have been several reports of the preparation of fragments of pituitary growth hormone which retain biological activity. An interesting example came from Chillemi and Pecile last year (*Experientia*, **27**, 385; 1971) who synthesized two peptides with growth promoting activity. Some doubt was thrown on this work, however, by the subsequent discovery that the amino-acid sequence of human growth hormone, on which the authors had based their synthetic work, was incorrect. In next Wednesday's *Nature New Biology* (August 23) Chillemi, Pecile and Aiello report the synthesis of two new peptides, according to the revised sequence.

The sequence of human growth hormone (a protein of 190 amino-acid residues) includes four partially duplicated regions. Chillemi *et al.* prepared peptides corresponding to two of these regions (residues 87 to 123 and 124 to 155) by chemical synthesis using the solid phase method. Both peptides showed substantial biological activity when tested in a growth hormone bioassay (the "tibia test"). The work suggests that intact growth hormone

possesses at least two biologically active sites, and, as the authors point out, there may well be others.

The success of the synthetic approach of Chillemi *et al.* to the preparation of fragments of growth hormone is particularly important because it opens the way to the preparation of peptides corresponding to many different regions of growth hormone, as well as analogues of them. This should enable detailed structure/function relationships to be carried out with this hormone. Ideally future work should include a full characterization of the biological properties of the fragments as well as synthesis of further peptides.

The observation that peptides corresponding to quite small regions of growth hormone may retain biological activity suggests that such fragments may play a physiological part in mediating the actions of growth hormone. (Such a hypothesis was proposed for the diabetogenic actions of growth hormone by Bornstein.) Peptides with growth promoting activity might also be suitable for clinical use—and help relieve the current shortage of human growth hormone.

Aerodynamics at NPL, 1917–1970

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The removal of the low density wind tunnel from the National Physical Laboratory (NPL) to the Royal Aircraft Establishment in December 1971 constituted the first step in the movement of several important aerodynamic test facilities, and provides an opportunity for Dr R. C. Pankhurst, Superintendent of the NPL Aerodynamics Division from 1964 to 1970, to recall briefly some of the contributions made by the division to the advancement of its subject.

ORIGINALLY a part of the NPL's Engineering Department, the Aerodynamics Division became a department in its own right in 1917. The staff brought with them experience in experimental aerodynamics dating back to 1903, when wind tunnel measurements were made on thin plates, lattice work, cylinders, and models of roofs and buildings; specifically aeronautical investigations started in 1909. When it was part of the Engineering Department, the aerodynamics team was headed by Bairstow, who, however, left the NPL in May 1917 to take up an appointment in the Air Ministry (and later to go to Imperial College as Zarahoff Professor of Aviation in the University of London); Stanton then superintended the Aerodynamics Department as well as the Engineering Department until the appointment of Southwell as Superintendent of the Aerodynamics Department in 1920. Subsequent superintendents were Relf (1925 to 1945), Fage (1945 to 1953), W. P. Jones (1953 to 1964) and Pankhurst (1964 to 1970). In the context of the historical development of aeronautics, it is relevant also to recall the names of the senior staff in 1917: Stanton; Relf, Pannell, Fage; Stedman (on active service), Bryant, Lavender, Irving, Cowley, Simmons; Frazer, Levy, R. Jones. At that time the division had a scientific staff of nineteen.

The secrecy that necessarily surrounded most of the work carried out during the First World War was lifted in 1919 to reveal the considerable advances that had been made in theoretical and practical aspects of the stability of aeroplanes, airships, kite balloons and parachutes, together with developments in techniques for scale model testing in wind "channels" (tunnels) and systematic investigations of the aerodynamic characteristics of wings, ailerons, screw propellers and complete aircraft models. Although the work quite properly included extensive tests of a rather *ad hoc* character, every endeavour was made to increase the value of

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such investigations by relating them to an organized theme of research; this policy was followed throughout the division's history, together with the complementary approach of selecting research topics largely by reference to the prospects of their practical application. It is relevant to note also the NPL's close cooperation throughout with the Royal Aircraft Establishment and the valuable element of friendly rivalry between the two organizations; formal coordination was provided by joint supervision of research programmes at management and headquarters level, as well as through the Advisory Committee for Aeronautics (later the Aeronautical Research Council), whose office had been established at NPL in 1909. (The secretary since 1920—when J. L. Nayler took over—and many successive secretaries of various committees and subcommittees, were drawn from the scientific staff of the NPL Aerodynamics Department.)

During the 1920s¹ the department undertook extensive investigations of the stability of new aircraft projects, including (in 1922) the first stability measurements to be made in a wind tunnel on a complete model with airscrew running (Fig. 1). At about this time the department also took part in international trials of wind tunnel models of aerofoils and airships: in the airship field it had completed extensive investigations before airship activities in Britain were finally stopped in 1931. A highlight of aeronautical history during this period was the series of Schneider Trophy contests, the last of which (1931) was won by Great Britain at a speed of 340.1 mile h⁻¹; a few days later a record speed of 407.5 mile h⁻¹ was established by the winning machine with an engine of increased power. These achievements of the pilots and the manufacturers of airframes, engines and airscrews were fully supported by research and development at Air Ministry establishments and at the NPL, where Cowley of the Aerodynamics Department made full investigations of the aerodynamic characteristics of large scale complete models in the 14 foot×7 foot ('Duplex') tunnel. The work for the 1931 contest concentrated chiefly on the reduction of the drag of the seaplane floats, the aerodynamics of the internal cooling of wing radiators, problems of yaw control during taxiing, and the performance of the screw propellers.

Propeller ("airscrew") studies provided a continuing research and development field at NPL for many years. In the 1920s the experimental work centred on wind tunnel tests of geometrical "families" of airscrews, whilst the theoretical work was based on simple blade-element theory until Goldstein's classic paper of 1929 "On the Vortex Wake of a Screw Propeller", which C. N. H. Lock at NPL rapidly developed into a form suitable for routine engineering application; this was later further developed into practical graphical (1934, 1938) and numerical (1941 to 1945) forms, which were widely used. It was also extended to embrace contra-rotation, as were parallel wind tunnel studies of propeller performance (Fig. 2). These investigations, and the deriva-

tion and application of blade-section data in high speed flight conditions (1940 to 1945), were necessitated by the rapid rise in engine power and in the speed of fighter aircraft; shaft horsepower of more than 2,000 had to be absorbed by propellers of diameter little more than 10 foot and at resultant tip speeds close to the speed of sound.

One of the principal challenges of the pioneering days of aeronautics was the need to devise appropriate experimental techniques. Outstanding among these was the measurement of airspeed to the required degree of accuracy, a subject highly appropriate to the NPL in its role of national standardizing laboratory. A great deal of the British work on the design of Pitot-static tubes and vane anemometers was done there, notably by Ower², together with pioneering work on hot wire anemometry (by Simmons). Later work concerned the effects of shock waves on the reading of a static pressure tube in high speed flow, and developments in hot wire anemometry and the associated data processing techniques that were required for measuring turbulence characteristics of a complicated character, such as various correlation functions and energy spectra. Other important novel techniques were also devised and are now widely used³, including Holder and North's applications of schlieren and shadowgraph methods to the visualization of high speed flow, associated techniques in high speed photography, methods of boundary layer flow visualization, and Preston's method of using a surface Pitot tube for measuring local skin friction. More recently, various techniques were evolved for investigating hypersonic flows of very short duration (a few ms) and for the study of low density aerodynamics. Right from the start, the division was provided with its own workshop staff, whose contributions were vital to the success of many technique developments and experimental investigations.

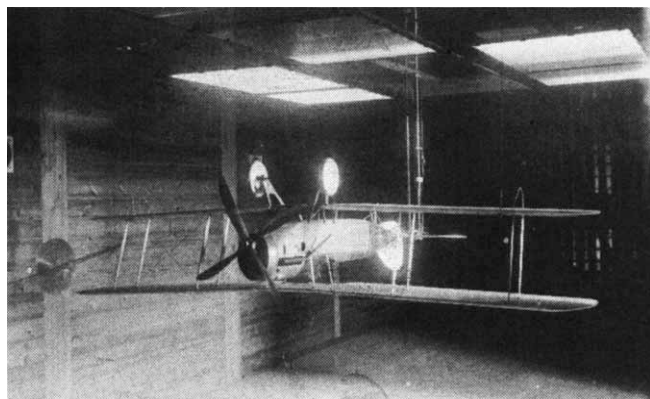


Fig. 1 Aircraft performance tests. 1/5 scale model of Bristol fighter aeroplane in the 14 foot $\times$ 7 foot ('Duplex') wind tunnel (maximum speed 100 foot s^{-1}). This was the first model to be tested in Britain with propeller running, a feature made possible by Relf's design of an electric motor that was powerful enough to drive the propeller and small enough to be housed within the fuselage. The model was suspended, inverted, from the tunnel's overhead balance for measuring the aerodynamic forces and moments (1922).

By 1925 several aeroplane accidents were recognized to have been a consequence of flutter (a flexural/torsional oscillatory instability caused by the interaction of aerodynamic with structural elastic and inertial forces), and in that year the Accident Investigation Sub-Committee of the Aeronautical Research Council recommended that a thorough study should be made so as to provide aircraft designers with the information needed to prevent any recurrence. A preliminary theoretical treatment by Frazer appeared within months; within a year both he and Duncan reported on

wind tunnel studies, and these were followed some eighteen months later by the classic Frazer-Duncan monograph⁴ which laid the foundations on which all subsequent British work in this field was based. Having established that flutter is not a resonance effect but an aeroelastic instability (though the term "aeroelastic" is of later vintage), the monograph presented detailed analytical and wind tunnel investigations and derived design recommendations for the prevention of wing flutter: safest of all, as Frazer and Duncan recognized, would be an irreversible aileron control, as suggested by Southwell. Less than three years later the same authors issued a second monograph⁵, which developed the subject further for monoplane wings and extended it to the flutter of biplanes and of tail units. An important by-product of the analytical work was the publication in 1938 of a treatise on matrix algebra⁶. Other important monographs on flutter research were published subsequently by Scruton⁷ and by J. Williams⁸.

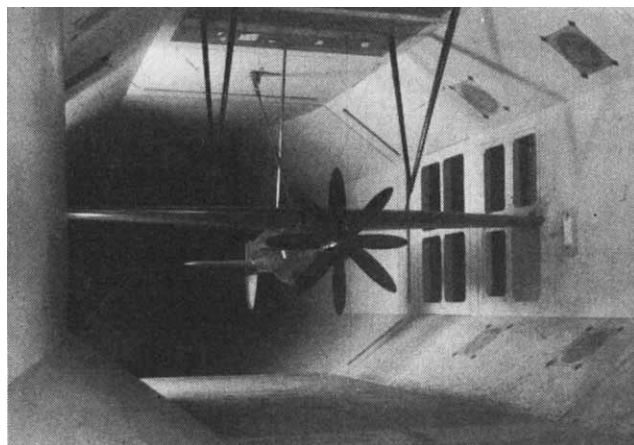


Fig. 2 Propeller research. Contra-rotating airscrews on a "Typhoon" aircraft model (1945).

Wind tunnel determinations of flutter speeds necessitated the development of models that were scaled correctly in respect of elastic and inertial properties as well as being geometrically similar to the prototype; theoretical predictions needed values of the various aerodynamic derivatives (rates of change of aerodynamic force and moment coefficients with respect to linear and angular displacements, velocities and accelerations), which in turn have to be calculated or determined experimentally. It was on the calculation and measurement of aerodynamic derivatives (of increasing complexity to meet the needs of increasingly severe flight conditions) that the later NPL work^{9,10} was concentrated (W. P. Jones, H. C. Garner and Lambourne). An important related investigation during recent years established the physical mechanism of aileron "buzz" in transonic flow: this involved the determination of the relationships between the geometrical motion of the control surface, the cyclic variations in the position and strength of the shock wave, and their effect on boundary layer thickness and flow separation.

The year 1929 was of further importance in the history of aeronautics for the publication of the classic paper by B. M. Jones (of Cambridge) on the feasibility of greatly reducing aircraft drag by systematic applications of knowledge of streamline flow. This led in turn to the study of the mutual interference (usually adverse) between the flow fields of the various components of an aeroplane, as a consequence of which two bodies close together may have a combined drag considerably greater than the sum of their individual drags as separate entities. Extensive studies at

NPL were described in a monograph by Ower⁶ published in 1932, which dealt especially with body-wing interference, nacelle-wing interference, and airscrew slipstream effects. About this time, too, a member of the staff of the Aerodynamics Division conceived the idea of an annular aerofoil designed to reduce the drag of radial air-cooled engines: this device (the "Townend ring") found extensive application.

With increasing refinements in aircraft design¹² it became important to obtain more precise knowledge of the way in which performance varied with Reynolds number, and to construct test facilities capable of achieving Reynolds numbers far closer to those of full scale than were attainable in the atmospheric tunnels available. To this end the NPL designed a tunnel with a working section of diameter 6 foot in which high Reynolds numbers were obtained by pressurization up to 25 atm. This facility (the compressed air tunnel, 1931, due to Relf) thus provided the invaluable capability of varying Reynolds number over a wide range as well as achieving a high maximum value of this parameter. This made possible the study of the variation of surface friction drag (by then the chief part of the total drag of a fighter aircraft, the "induced" drag—the drag that arises for any lifting wing, even in inviscid flow—amounting to no more than some 5% of the whole), the effects of surface roughness, and the performance at high Reynolds numbers of slotted wings, split flaps, and other devices for increasing maximum lift. Models of new prototypes were also frequently tested in this tunnel.

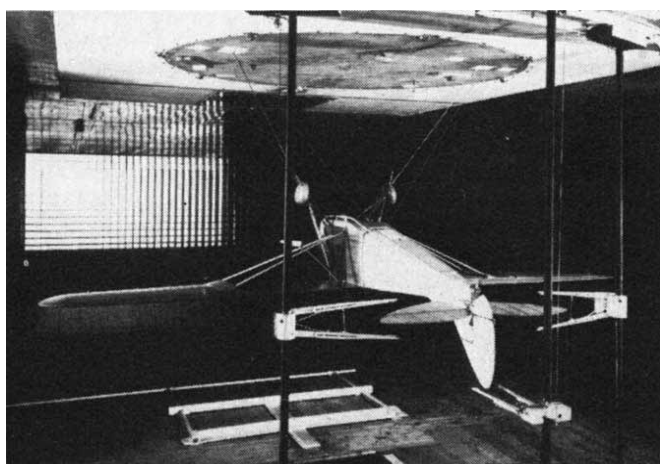


Fig. 3 Flutter investigations on a "Puss Moth" aeroplane. The tail unit was an aeroelastic replica of the prototype; three "grabs" ensure that the wind induced oscillations of the tail surfaces and rudder do not reach excessive amplitudes (1934).

Another important area of work during the 1930s comprised pioneering studies of stream turbulence (in association with G. I. Taylor); these necessitated the development of the hot wire anemometer, which still remains—with greatly improved electronic circuitry—the principal experimental tool in this notoriously difficult field, and the construction of a wind tunnel with a very large contraction ratio and hence with very low turbulence levels. Turbulence in pipe flow and within boundary layers was also studied, particularly by Fage. Turbulence investigations were interrupted by the Second World War, but were resumed in the 1960s, in both boundary layer and jet flows, by Bradshaw. In particular, recognition of the need for more powerful—and physically better founded—methods of calculating the development of turbulent boundary layers led Bradshaw to formulate and develop an important new approach¹³, which assumes a unique relation between the turbulent motion and the shear stress profile, and regards the turbulent energy

equation as one to be solved for the rate of change of turbulent kinetic energy (and hence of turbulent shear stress) along each streamline. The method is applicable to boundary layers with suction or injection, and on rough surfaces, and has been extended to embrace compressible flow, heat transfer, unsteady flow, wakes, and three-dimensional conditions.

The division's first high speed tunnel was constructed in 1934. It was of the induced flow type, and operated at first from the high pressure air supply provided by the compressed air tunnel when it was being decompressed. This tunnel, and a later (20 inch × 8 inch) tunnel with adjustable streamline walls, were for a long time the only ones in Britain suitable for the high speed aerofoil research begun by C. N. H. Lock and Hilton. The whole complex of high speed tunnels devised later by Holder¹⁴ were likewise mostly of the induced flow type (together with several direct discharge tunnels) and were powered by air stored at 25 atm (the maximum working pressure of the compressed air tunnel), with vast storage capacity. Both types of intermittent facilities afford great economy of peak load and flexibility of operation.

Meanwhile work had continued during the 1930s on various forms of flutter, including detailed studies of the "Puss Moth" aeroplane (Fig. 3), together with investigations (by Bryant and Irving) of aircraft stability and control and—until 1935—on spinning. The mid-1930s brought with them a slowing down of the longer term research in order to respond more effectively to the needs of the Royal Air Force. The provision of high speed tunnels formed part of this scene; and by the early 1940s the division possessed also several new low speed tunnels of then modern design, and, somewhat belatedly, a new whirling arm (in 1945).

The division's activities during the war years¹⁵ included wing section design for various aircraft, stemming from the ability to shape aerofoils to give specified pressure distributions¹⁶ (a facility which was provided by Goldstein, seconded to the NPL from Cambridge for the duration, together with Lighthill's exact method) combined with test equipment for studying aerofoil behaviour up to high subsonic speeds. The prime consideration, as aircraft speeds increased, was to increase the Mach number above which the drag coefficient inevitably increases. The advantages of preserving a long run of laminar flow were also recognized, although difficulties in maintaining sufficiently high standards of surface finish and surface cleanliness prevented their possibilities from being fully realized in practice. Low drag suction aerofoils were also developed, in particular thick slotted aerofoils as originally proposed by A. A. Griffith; these were not, however, adopted in practice, not only because of problems of surface finish, but also because of their low critical Mach number. Other wartime work included the development of methods of calculating wing loading (by Falkner); detailed studies of the various factors that determine aircraft control effectiveness, of gust effects, and of "snaking"; investigations of spring tab controls, of tail flutter and of rudder flutter; the measurement and theoretical prediction of aerodynamic flutter derivatives; and the development and application of methods of predicting the performance of propellers for high speed aircraft. As aircraft speed increased still further, attention was also turned to aerodynamic problems of flight above the speed of sound: Lighthill formulated his theory of the flow past wings and bodies at supersonic speeds¹⁷, and the conversion of the 12 inch circular tunnel to supersonic operation (towards the end of the Second World War) produced the first schlieren and shadowgraph photographs to be obtained in Britain of the flow past aerofoils at Mach numbers greater than unity.

The study of boundary layer control (particularly using area suction rather than suction through slots, and also using slot blowing to increase maximum lift) continued into the

mid-1950s. Especially notable for its fundamental importance was area suction as a means of generating flow fields which provided close practical approximations to those of potential flow theory, as in the production of lift on a circular cylinder using a Thwaites flap. And the development of blowing over flaps (J. Williams) led to important practical applications to production aircraft, particularly the Vickers (Supermarine) "Scimitar" and the Blackburn "Buccaneer"

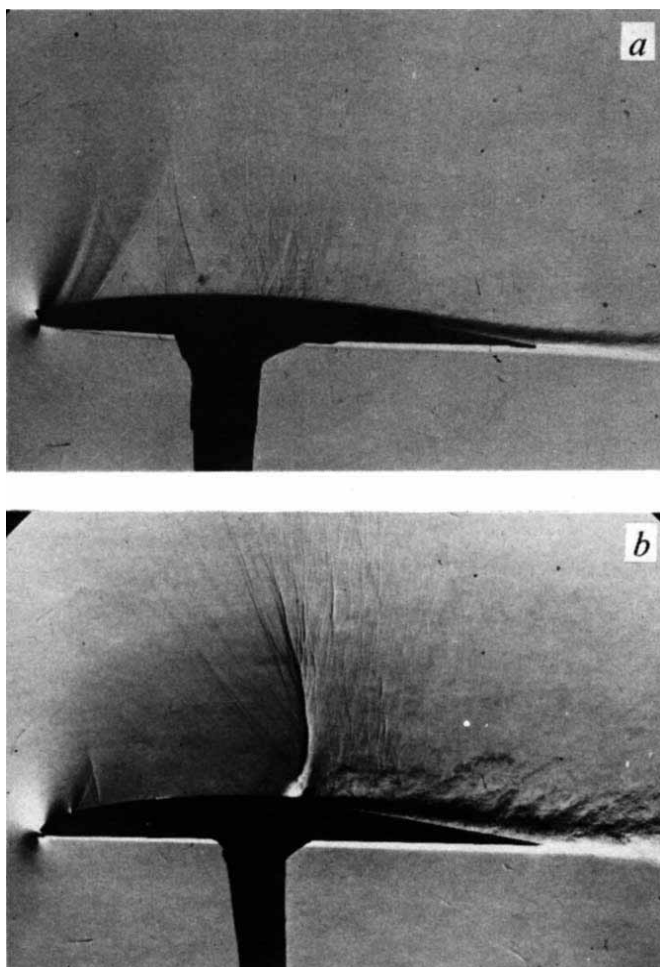


Fig. 4 Transonic flow. Elimination of strong, drag-producing shock waves and of shock-induced boundary layer separation on a two-dimensional wing section by designing its profile in such a way as to produce a "peaky" velocity distribution (a) instead of that of the conventional shape (b). The test conditions were a Mach number of 0.73 and a lift coefficient of 0.77 (1963).

The advent of swept wings towards the end of the Second World War, with their promise of delaying the onset of adverse compressibility effects until considerably higher forward speeds—as these effects are largely determined by the velocity component normal to the leading edge of the wing—led to a great deal of theoretical and experimental work by H. C. Garner and R. C. Lock on wing loading for such configurations, on their problems of stability and control, and on the design of wing sections^{18,19} to meet industrial requirements: much of this work was based on extensive studies (by Holder, Pearcey and Rogers) of the mechanism of the interaction between shock waves and boundary layers, especially shock induced separation of the boundary layer, and of its adverse effects in limiting the Mach number and altitude at which an aircraft can operate safely or in restricting manoeuvrability at a given altitude and Mach

number. For one aircraft, special shapes of leading edge to delay separation were developed in collaboration with the firm and the RAE, whilst shock induced separation on existing wing shapes was successfully prevented for several aircraft designs by means of vortex generators. Recent swept winged aircraft to which NPL wing section design methods have been applied include the VC 10, "Trident", BAC 111, HP "Jetstream" and HS "Harrier". One of the principal objectives of swept wing design in three-dimensional flow²⁰ was to devise a geometrical configuration that would result in isobars that followed the geometrical sweep, and to make them do so right into the junction between the wing root and the fuselage: in lifting conditions this was achieved by combining wing twist with fuselage waisting to a different extent on upper and lower surfaces of the wings.

Outstanding developments in the design of wing section shapes were Pearcey's concept of "peaky" aerofoils and his exploitation of finite thickness at the trailing edge. On a "peaky" section the local surface velocity is allowed to become supersonic near the leading edge, the pressure distribution further aft being controlled through the "reflexion" of expansion waves, as compressions, from the sonic line above the wing surface; and it was along these lines that aerofoil shapes were derived that secured practically shock-free recompression (Fig. 4)—an important step towards settling the so-called "transonic controversy". The use of non-zero thickness at the trailing edge provided a means of delaying the onset of drag rise and shock induced boundary layer separation, and was accompanied by studies of means of reducing the associated base drag. Rather surprisingly, high speed aerofoil research of the type pursued at NPL had been allowed to lapse in the early 1950s in most other aerodynamics research laboratories, at least in the West; when it was taken up again some fifteen years later, the NPL found itself the focus for related work in Britain and an important link with countries overseas. For such investigations as these the experimental capability of the division was considerably extended in respect of both Mach number and Reynolds number by the provision of several new high speed tunnels, and for research in heat transfer at Mach numbers from 2 to 5 a continuously-running 6 inch×6 inch tunnel was commissioned which provided a wide range of stagnation pressure (up to 25 atm absolute) and stagnation pressures up to 450° C.

The ten years following the Second World War were also highly formative in another important respect. In 1946 a suspension bridge was being planned for crossing the Severn estuary, and because the failure of the Tacoma Narrows Bridge in 1940 was known to have been due to aeroelastic instability, the designers of the new project turned naturally to the NPL flutter team for guidance. Thus began the extensive investigations²¹ by Frazer and Scruton on an unprecedentedly detailed complete aeroelastic model (Fig. 5a) leading also to the development of the method of testing sectional models that has since become the cornerstone of all subsequent work in this field. The reputation established in this way caused subsequent aerodynamic problems of civil engineering structures to be referred to the team led by Scruton at NPL, which then became the British centre for research and *ad hoc* investigations on the aerodynamics of bridges, stacks, towers and other structures of civil engineering—a field which, together with certain other non-aeronautical areas such as the airflow over landscapes, over the superstructures of ships and from funnels and chimneys, has become known as "industrial" aerodynamics. Much of the civil engineering aerodynamics is concerned with various types of wind induced oscillations, and it is pertinent to recall the invention in 1957 of the helicoidal strake device for preventing oscillations of a circular chimney stack or similar structure (Fig. 5b) followed by the perforated shroud for the same purpose, and to note the subsequent application of the shroud device to prevent oscillations of steel piles in

flowing water. These were specimens of the type used for a jetty at Immingham in the Humber estuary: during the construction of the jetty an isolated pile had attained an amplitude of about 3 m (and then failed) in fast tidal flow, and whole segments of the jetty, weighing hundreds of tons, had oscillated alarmingly with amplitudes of several inches.

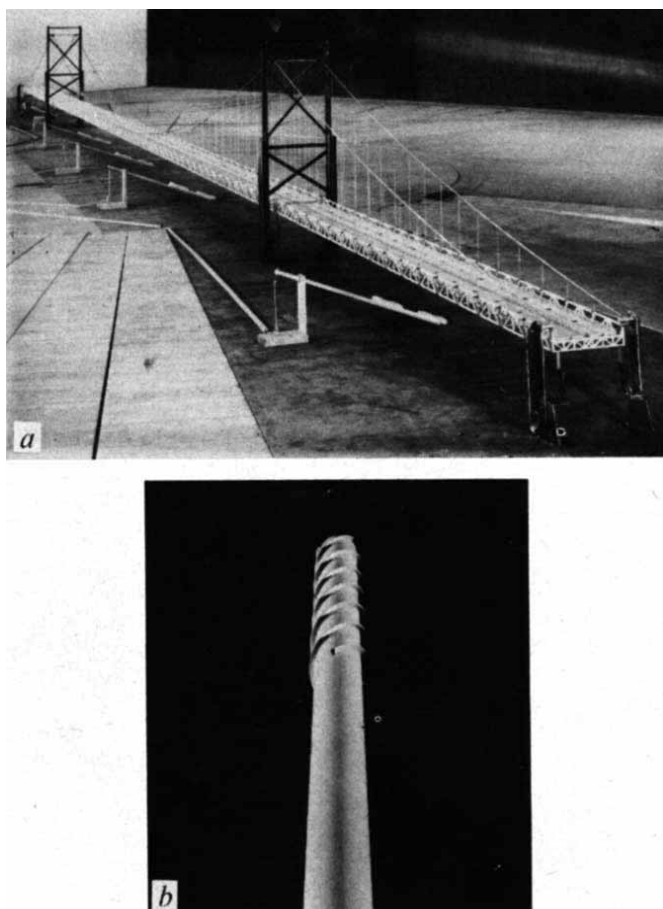


Fig. 5 "Industrial" aerodynamics (civil engineering structures, smoke dispersal and so on). *a*, A complete aeroelastic model of the design initially proposed for the Severn Bridge in a specially constructed wind tunnel, 60 foot wide, at Thurleigh (1948). The chief features of the design were incorporated in the Forth Road Bridge, as a novel form of road-deck construction was developed for the Beachley-Aust crossing as finally built in 1966. *b*, Prevention of wind induced oscillations of tall stacks by means of helical strakes. Photograph shows strakes fitted to a circular cylinder representing a circular chimney stack (1957).

The original Severn Bridge studies of 1946 to 1950 were in fact applied to the Forth Bridge of 1964, the Severn project having been delayed by cuts in capital expenditure; when the Severn crossing was finally authorized, a fresh investigation was undertaken in order to study the aerodynamic characteristics of the novel steel-plated box structure adopted for the roadway deck in place of the former top-deck truss-stiffened design, so as to establish erection procedures that would be safe in respect of wind loads and aerodynamically induced oscillations. As far as experimental equipment was concerned, for many years the wind tunnels available for industrial aerodynamics dated back to the 1920s and 1930s, but a more recent tunnel, reconstructed to have a working section 7 foot $\times$ 7 foot, was devoted entirely to industrial aerodynamics from 1960 onwards. About this time also, the compressed air tunnel began to be increasingly used for tests of cooling towers, circular cylinders (including, later, models of the Immingham piers) and other industrial aero-

dynamics investigations in which scale effect was expected to be significant. The validity of model scale tests of the airflow over the superstructures of ships, and of the dispersal of smoke from funnels, received valuable confirmation from comparisons with full scale observations made in 1961 on SS Oriana and SS Canberra.

Further activities in industrial aerodynamics included the first International Conference on Wind Effects on Buildings and Structures, held at NPL in 1963, the provision of a forum for regular meetings of those concerned with industrial aerodynamics throughout Britain (from 1964 onwards), and repeated requests (which, however, were not granted, because of financial stringency) in the 1960s for a tunnel specifically designed to suit exactly the special requirements of industrial aerodynamics testing. Since about 1964 the Industrial Aerodynamics Section has devoted an increasing amount of effort to longer term research, in particular to the effects of stream turbulence and wind profile on wind loading and aerodynamic excitation and to vortex shedding from tapered cylinders.

The challenging problems of hypersonic flow (conventionally regarded as flow at free stream Mach numbers above 5) led to the division's first shock tube in 1956, together with the beginning of the development of the short duration instrumentation needed for making measurements in extremely short running times (of the order of a few ms). A larger shock tunnel followed the next year, as did also the White Paper on Defence (Cmd 124) which announced the government decision not to go ahead with the development of a supersonic manned bomber but to develop instead a ground-to-air missile defence system to replace the manned aircraft of Fighter Command. This emphasis on ballistic and guided weapons was reflected in increasing effort devoted to hypersonic flow over the next six or eight years, during which the division built up a range of facilities second to none in Europe. These included small shock tubes for optical investigations of shock wave properties and interactions, for microwave determinations of electron density and collision frequency, and for investigations in chemical kinetics; larger shock tunnels, for aerodynamic investigations; an arc driven hot shot tunnel; a helium tunnel; and a low density tunnel for simulating supersonic and hypersonic flight at altitudes of 20 to 70 miles. Specific research topics studied in these facilities (under Holder until he went to Oxford as Professor of Engineering Science) were concerned with problems of cruising flight at high Mach numbers and high altitudes (Fig. 6) at which heat transfer effects are of great aerodynamic importance, and with the influence of dissociation, radiation and viscous interaction at atmospheric re-entry. Theoretical topics included hypersonic small disturbance theory and non-equilibrium nozzle flow (expanding flow in a relaxing gas). From 1965 onwards, however, official support for research in hypersonic flow was greatly reduced because it was felt necessary to concentrate Britain's limited resources into areas of greater immediate need, especially as it seemed unlikely that Britain would embark on the construction of hypersonic transport aeroplanes. Accordingly, in 1966, the division's work on high temperature gas physics was brought to a close; the rest of the hypersonic flow effort was subsequently steadily reduced and several of the facilities were closed down so that the remaining effort was centred on only the 16 inch shock tunnel, the shock/gun tunnel, the helium tunnel and the low density tunnel. Although constituting a much reduced range as regards simulation capability, these facilities provided reasonable coverage of the chief problem areas of practical and potential engineering importance to the aircraft industry. An example of forward looking research in the 16 inch shock tunnel is shown in Fig. 7.

Other changes in the division's research programme that were made consistently with developments in the government's aircraft policy were reductions in the total effort on aircraft aerodynamics from 1966 onwards (accompanied by a

further build-up in industrial aerodynamics) and rather greater emphasis on shorter term research. One consequence of this was the decision, also in 1966, to bring to a close some fifteen years of outstanding research, led by Stuart, which culminated in a non-linear theory of the flow instability that generally precedes transition to turbulence, and which is an essential feature in the initial growth of small disturbances from infinitesimal to finite values. In the closing stages of this work the way was paved to further advances by devising a computer program for solving the Orr-Sommerfeld equation (the disturbance equation which governs a large class of flows but which had defied attempts at satisfactory analytical solution for over half a century) for flows both without and with heat transfer.

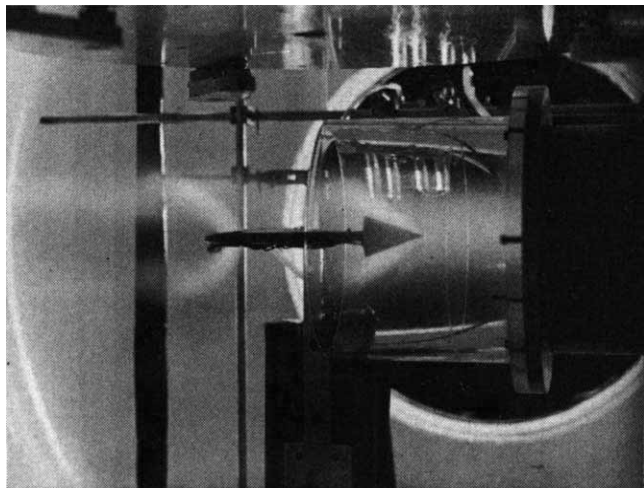


Fig. 6 High altitude aerodynamics (rarefied gas dynamics). Flow is about a 60° cone at twice the speed of sound and a free stream pressure of $25 \mu\text{m Hg}$, and is made visible by the after-glow technique (1962). The low density wind tunnel in which this photograph was taken was dismantled in December 1971 and re-erected at the Royal Aircraft Establishment, Farnborough, in January 1972.

NPL's Acoustics Section under D. W. Robinson was attached to the Aerodynamics Division in November 1966. Its main research areas concerned psychological and physical acoustics: specific topics included bone conduction thresholds, hearing impairment caused by prolonged exposure to noise, hearing conservation criteria, traffic and aircraft noise (which led to the novel concept of "noise pollution level"), sound propagation and measurement, and international standardization of audiometric data and instruments. The section played a notable part in devising a certification scheme for the noise from subsonic aircraft in the neighbourhood of airports, and developed simplified methods for calibrating vehicle noise meters in connexion with the statutory regulation of noise emitted by motor vehicles that came into force in 1968. In 1970 the results were published of an extensive investigation²², embodying five years of field work and carried out in collaboration with the Medical Research Council, of the effects of industrial noise on hearing: these studies led to the further concept of noise "immission", established relationships between permanent hearing loss and temporary threshold shift, and opened up the possibility of differential diagnostic techniques for identifying those subjects who are likely to be unusually susceptible to deafness induced by noise.

In May 1970 a decision of the Minister of Technology decreed the transfer of all the division's aircraft aerodynamics to the Royal Aircraft Establishment, leaving industrial aerodynamics and acoustics at NPL to form the so-called Environmental Unit, later incorporated in the Division of Maritime

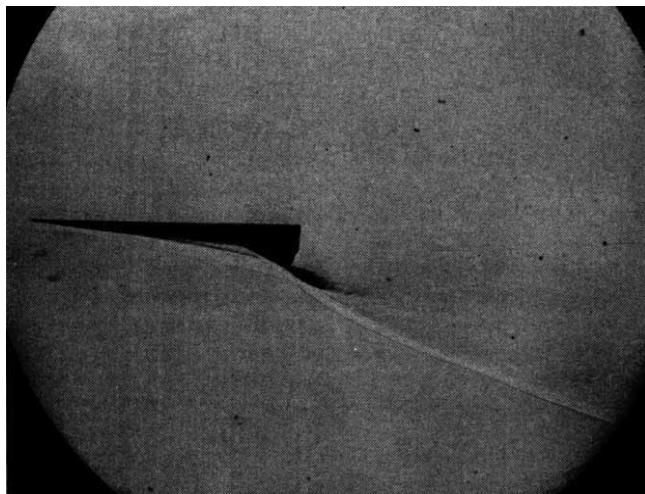


Fig. 7 Hypersonic flow. The model shown has delta planform and deflected trailing edge flap; it is in free flight at 8.6 times the speed of sound in the NPL 16 inch shock tunnel (1970).

Science: the sizes of the respective areas at this stage are indicated by the figures of twenty in the scientific officer grades engaged on aircraft aerodynamics, together with four serving the Aeronautical Research Council and twelve in the Environmental Unit. The movement of aircraft aerodynamics staff to Farnborough and Bedford began in October of that year (1970), when a new structure for the enlarged RAE Aerodynamics Department was brought into operation. The outline scheme for moving facilities from Teddington had also then been prepared, and provided for the transfer of those items of equipment that were complementary to the tunnels at Farnborough and Bedford. Accordingly NPL's work on aircraft aerodynamics—which for several years had already been carried out on the basis of a joint RAE/NPL programme monitored by meetings between Mintech (Air), the two establishments and the aircraft industry—came under single (RAE) management with the object of ensuring a more efficient long term overall deployment of Britain's limited resources. Having maintained an international recognized reputation for more than fifty years, NPL's Aerodynamics Division was thus brought to a close.

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MSI and MSII made on Ribosome in Idling Step of Protein Synthesis

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The unusual guanosine nucleotides, MSI and MSII, accumulated *in vivo* during amino-acid starvation of stringent strains of *E. coli* are shown to be synthesized *in vitro* as a product of an idling step in protein synthesis occurring on the ribosomes.

THE synthesis of stable RNA species in many *Escherichia coli* strains is sharply curtailed by deprivation of a required amino-acid¹⁻⁴. This control mechanism, called the stringent response, depends on the function of the *rel* gene. Mutations in this gene give rise to relaxed mutants¹, which continue to accumulate RNA for a considerable time after amino-acid deprivation. Cashel and Gallant^{5,6} found that amino-acid starvation causes a rapid accumulation of two unusual guanosine nucleotides, called "magic spots" I and II (MSI and MSII), in stringent (*rel*⁺) but not in relaxed (*rel*⁻) strains. They postulated⁵ that high intracellular concentrations of the MS compounds led to the cessation of RNA accumulation and to the other characteristics of the stringent response: inability to incorporate uracil from the medium⁷, shrinkage of the nucleoside triphosphate pools⁷⁻⁹, and inhibition of the synthesis of glycolytic esters¹⁰. Cashel and Kalbacher¹¹ have identified MSI as a guanosine tetraphosphate (ppGpp, 5' diphosphate 3' or 2' diphosphate guanosine) and MSII as a guanosine pentaphosphate.

We report here that MSI and MSII can be synthesized *in vitro* on the ribosome using GTP (or GDP) and ATP as substrates, and that the difference between relaxed and stringent strains with respect to MS accumulation during amino-acid starvation is due to an alteration in a protein factor present in the 0.5 M NH₄Cl ribosomal wash.

MSI and MSII synthesized *in vitro*

MSI and MSII are synthesized *in vitro* in a reaction containing the components listed in Table 1. This simple reaction requires, in addition to buffer and salts, only the substrates GTP (or GDP) and ATP, high salt washed ribo-

Table 1 Composition of *in vitro* MSI and MSII Synthesizing System

Component	Amount/50 μ l. reaction
Tris-acetate, pH 7.8	42 mm
Dithiothreitol	1.4 mm
Magnesium-acetate	11.4 mm
Ammonium-acetate	27.0 mm
GTP	0.55 mm
ATP	2.2 mm
Potassium-acetate	10.0 mm
High salt ribosomes	100 μ g
α - ³² P-GTP	1 μ Ci
0.5 M NH ₄ Cl ribosomal wash	7 μ g

The ribosomes and ribosomal washes were prepared as follows. CP 78 *rel*⁺ (obtained from the strain collection at Yale through Peter Lengyel) was grown to a cell density of 5×10^8 cells/ml. at 34° C in a medium containing (per litre) 5.6 g KH₂PO₄ (anhydrous); 28.9 g K₂HPO₄ (anhydrous); 10 g yeast extract; 10 mg thiamine; and 1% glucose (the medium described by Zubay *et al.*²⁵). The cells were chilled and collected at 7,000g for 20 min and washed twice by resuspending the pellet in four times the pellet volume of buffer A (0.01 M Tris-acetate, pH 7.8, 0.014 M Mg-acetate, 0.06 M K-acetate and 10⁻⁴ M dithiothreitol) and recentrifuging. Finally, the cells were resuspended in buffer B (buffer A, with 10⁻³ M dithiothreitol); 4 μ g/ml. of DNAase (Worthington) added, and the cells broken in an 'Aminco' pressure cell using pressures between 5,000 and 10,000 p.s.i. The lysate was stirred gently for 30 min at 4° C and centrifuged at 30,000g for 20 min to remove debris. These "S-30" crude extracts were centrifuged in a Beckman angle 40° rotor for 3 h at 40,000 r.p.m. at 4° C. The supernatant was decanted and the ribosomal pellet rinsed with buffer B and resuspended in the same buffer. The resuspended ribosomes were layered above an equal volume of buffer B made 40% in sucrose and centrifuged at 40,000 r.p.m. for 12 h in an 'International A-170' rotor at 4° C. The supernatant was decanted and the pellet washed an additional time with buffer B by resuspending it and centrifuging at 40,000 r.p.m. in an angle 40 rotor for 2 h. This pellet was resuspended in one-fourth the original "S-30" volume to give a final concentration of ribosomes between 30 and 60 mg/ml.

The 0.5 M NH₄Cl wash was made by centrifuging ribosomes (60 mg/ml.) at 10,000g to remove aggregates and then pelleted for 2 h. They were then resuspended at 60 mg/ml. in buffer B made 0.5 M in NH₄Cl. The resuspended ribosomes were gently shaken for 2 h at 4° C and pelleted again. The supernatant was decanted and centrifuged once again for 2 h at 40,000 r.p.m. in the angle 40 rotor. This supernatant was the source of the 0.5 M NH₄Cl ribosomal wash. The ribosomal pellet was washed twice more in a large volume of the 0.5 M NH₄Cl buffer, and finally resuspended at 120 mg/ml. in buffer B and used as the 0.5 M NH₄Cl washed ribosomes.

some which retain some G factor activity, and a factor present in the 0.5 M NH_4Cl wash of ribosomes extracted from stringent cells; we shall call this the stringent (str) factor. The preparation of the high salt washed ribosomes and the 0.5 M NH_4Cl wash is described in Table 1. The conversion of the substrates to MSI and MSII is followed by chromatography of the reaction products on thin layer polyethyleneimine (PEI) plates, which separate guanosine nucleotides according to the number of phosphates. In most experiments the GTP was labelled in the α position with ^{32}P .

Fig. 1 demonstrates that both the high-salt washed ribosomes and the 0.5 M NH_4Cl wash are needed for MSI and MSII synthesis. Neither of these two components by themselves can mediate the synthesis of these guanosine compounds. Only the 0.5 M NH_4Cl ribosomal wash from the *rel*⁺ cells contains the stringent factor. Furthermore, the addition of uncharged tRNA, Q β RNA and poly U does not affect the amount of MS compounds synthesized.

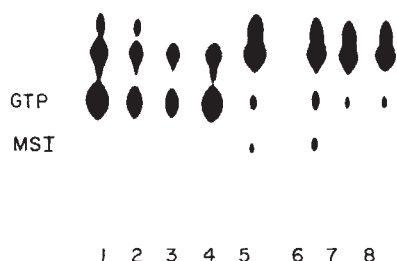


Fig. 1 A factor present in the 0.5 M NH_4Cl ribosomal wash from stringent strains is necessary for MS synthesis.

Reaction	0.5 M NH_4Cl washed ribosomes		0.5 M NH_4Cl M ribosomal wash	
	413 (<i>rel</i> ⁺)	415 (<i>rel</i> ⁻)	413 (<i>rel</i> ⁺)	415 (<i>rel</i> ⁻)
1	—	—	+	—
2	—	—	—	+
3	+	—	—	—
4	—	+	—	—
5	+	—	+	—
6	—	+	+	—
7	+	—	—	+
8	—	+	—	+

High salt washed ribosomes and the 0.5 M NH_4Cl ribosomal wash were prepared as in Table 1. The reactions contained the components listed in Table 1 in 50 μl , and were incubated at 37° C for 30 min. The reactions were terminated by chilling in ice and adding 1 μl of 88% formic acid. The reaction tubes were mixed vigorously on a vortex mixer and centrifuged in a clinical centrifuge at 3,000g for 5 min. The clear supernatant was transferred to clean tubes and 1.0 μl samples spotted on 'Brinkmann' polyethyleneimine (PEI) thin layer plates. The samples were dried, the plate rinsed with distilled water, dried again and developed with 1.5 M KH_2PO_4 , pH 3.4, as described by Cashel *et al.*³⁰. The plates were dried and autoradiographed by exposure to 'Kodak No-Screen' medical X-ray film. The spots in ascending order were MSII, MSI, GTP, GDP, GMP, and free phosphate. The identity of MSI and MSII has been confirmed by co-chromatography with authentic MSI and MSII prepared in bulk from cells as described by Cashel and Kalbacher¹¹ in two dimensions, first with 3.3 M ammonium formate and 4.2% boric acid (adjusted to pH 7.0 with NH_4OH) and then in 1.5 M KH_2PO_4 , pH 3.4. The rate of synthesis of the MS compounds is, as calculated from an experiment not pictured here, about 0.8 molecules of MS compounds/s/ribosome, assuming all ribosomes are active. The high salt washed ribosomes and 0.5 M NH_4Cl ribosomal wash were obtained from the stringent and relaxed isogenic pair of strains 413 (*rel*⁺) and 415 (*rel*⁻) (from the collection of D. Morse).

The elongation factor G^{12,13} is also necessary for the synthesis of the MS compounds. When the synthesis is attempted with ribosomes washed seven times in high salt, added G factor (provided by H. Weissbach) stimulated the

synthesis of MSI and MSII up to eight times. Stringent factor and the seven times washed ribosomes in our standard reaction mixture synthesized 0.9 nmol of MS compounds; when 6 μg of G factor was added, 7 nmol of MS compounds was synthesized. A small amount of G factor probably remains bound to the five times washed ribosomes, as has been reported by Nishizuka and Lipmann¹². The washed ribosomes and G factor alone do not make MSI and MSII without the stringent factor. Separate experiments have shown that the elongation factors Tu and Ts cannot substitute for the stringent factor.

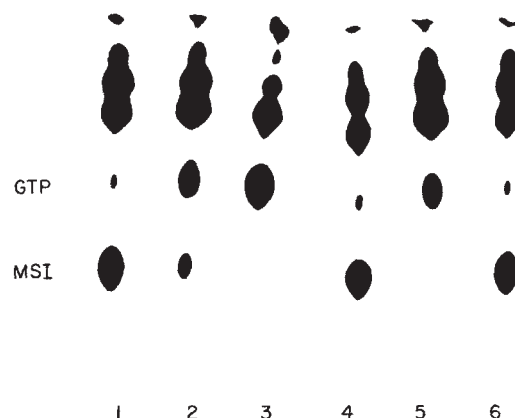


Fig. 2 Inhibition of MS synthesis by the antibiotics fusidic acid and thiostrepton.

Reaction	Fusidic acid	Thiostrepton
1	—	—
2	4×10^{-4} M	—
3	1×10^{-3} M	—
4	—	—
5	—	1×10^{-6} M
6	—	4×10^{-7} M

The conditions were as those described for Table 1. However, the ribosomes were not washed with high salt and retained the ability to synthesize the MS compounds. Fusidic acid was a gift of D. Goldéz and R. T. Garvin and thiostrepton a gift of B. Wallace. Both drugs were dissolved in 50% dimethylsulphoxide and the final concentration of this solvent in all reaction mixtures was 1%.

The dependence of the reaction on active G factor was further confirmed by inhibition experiments using fusidic acid or thiostrepton. Fig. 2 shows that concentrations of fusidic acid and thiostrepton which inhibit GTP hydrolysis and *in vitro* protein synthesis prevent the conversion of GTP to MS compounds. Tocchini-Valentini *et al.*¹⁵ and Kinoshita *et al.*¹⁶ have shown that fusidic acid interacts directly with the G factor, by finding that mutants resistant to fusidic acid have an altered G factor. Fusidic acid inhibits protein synthesis by stabilizing the G-GDP complex on the ribosome¹⁷ and thus preventing the binding of the Tu-aminoacyl tRNA-GTP complex to the acceptor (A) site¹⁸. Thiostrepton binds to the 50S subunit¹⁹ and blocks enzymatic and non-enzymatic translocation²⁰. This drug also inhibits the binding of both the Tu-aminoacyl tRNA-GTP and the G factor-GTP (or G-GDP) complexes to the ribosome²¹⁻²⁴. Thus, inhibition by both fusidic acid and thiostrepton and the requirement for G factor suggest that the synthesis of MSI and MSII is associated with the translocation machinery.

How MSI and MSII are Made

MSI and MSII are synthesized in the *in vitro* system by transfer of phosphates from ATP to GDP and GTP. ATP

is absolutely required for the synthesis of the MS compounds. We propose that MSII is the product of the reaction $5' \text{ pppG} + 5' \text{ pppA } 5' \rightarrow 5' \text{ pppGpp} (2' \text{ or } 3') + 5' \text{ pA}$, and the MSI is synthesized in the reaction $5' \text{ ppG} + 5' \text{ pppA} \rightarrow 5' \text{ ppGpp} (2' \text{ or } 3') + 5' \text{ pA}$.

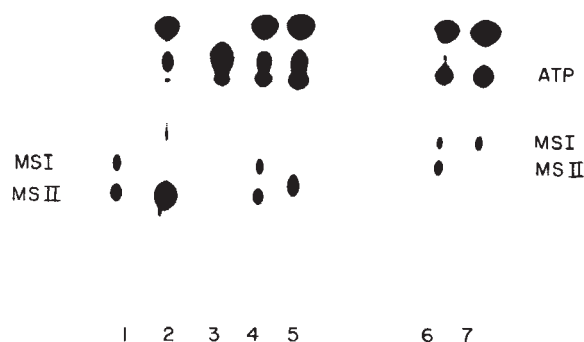


Fig. 3 MSI and MSII are synthesized from GDP and GTP using ATP.

Reaction	Unlabelled substrates	Labelled substrates
1	ATP	α - ^{32}P GTP
2	ATP	γ - ^{32}P GTP
3	GTP	α - ^{32}P ATP
4	GTP	γ - ^{32}P ATP
5	pcppG	γ - ^{32}P ATP
6	GTP	γ - ^{32}P ATP
7	GDP	γ - ^{32}P ATP

Reaction conditions as in Table 1. The stringent factor was further purified by precipitation with 33% $(\text{NH}_4)_2\text{SO}_4$ saturation. The γ - ^{32}P labelled $5' \text{ GTP}$ and $5' \text{ ATP}$ were prepared by E. Minkley and the α - ^{32}P labelled $5' \text{ ATP}$ and $5' \text{ GTP}$ were purchased from ICN and New England Nuclear. The β - γ methylene guanosine $5'$ triphosphate was purchased from Sigma Biochemicals and used at a concentration of 0.55 mM. The concentration of $5' \text{ GDP}$ is 0.55 mM in the experiment in which it replaces GTP. The specific activity of the ^{32}P labelled substrates was approximately 0.2 Ci/mmol.

A direct demonstration that phosphates are transferred from ATP to GDP and GTP is shown in Fig. 3. When γ - ^{32}P -ATP is added to a reaction mixture containing high salt washed ribosomes, partially purified stringent factor and cold GTP, the product of the reaction is predominantly MSII. When GDP is added instead of GTP, only MSI is formed. The α phosphate of ^{32}P -ATP is not transferred to either MSI or MSII. The absence of labelled MSI in a reaction involving γ - ^{32}P -GTP and nonradioactive ATP demonstrates that GTP does not donate the additional phosphates to form the MS compounds. The MSI produced in the reaction involving GTP arises in part because GTP is hydrolysed to GDP, but could stem from the degradation of MSII. When the β - γ bond is modified in the GTP analogue, pcpopG (β - γ methylene guanosine $5'$ triphosphate), the product is a single compound with a mobility on PEI plates (developed with 1.5 M KH_2PO_4 , pH 3.4) between those of MSI and MSII. This compound probably corresponds to the analogue of MSII (because in these chromatography conditions the methylene analogue, pcpopG, has a higher mobility than GTP. In our most highly purified system, over 90% of the product of reaction involving ATP and GTP is MSII.

The Stringent Factor

We discovered the stringent factor because the coupled *in vitro* protein synthesizing system developed by Zubay *et al.*²⁵

mimics (with respect to synthesis of MS compounds) the cellular response to amino-acid starvation. Table 2 illustrates an experiment in which extracts are prepared from a pair of strains which contain a deletion of the lactose operon, and are isogenic except for the *rel* locus. This makes it possible to assay for protein synthesis by measuring the amount of β -galactosidase synthesized when the DNA of a *lac* transducing phage is added as template to the reaction mixture. Extracts prepared from both the stringent and relaxed strain were active in protein synthesis. When a full complement of amino-acids is present in the reaction mixtures, both extracts make approximately the same amounts of β -galactosidase and no MS compounds accumulate. When the amino-acids were left out of the reaction mixtures, MSI and MSII accumulated when the extracts are prepared from stringent strains, not from relaxed strains; in both cases no detectable amounts of β -galactosidase are synthesized.

Table 2 Synthesis of MS Compounds in a Coupled *in vitro* Protein Synthesizing System

Reaction	Amino-acids	λ plac _s	Strain	OD ₄₂₀ /20 h	nmol MSI and MSII
1	+	—	<i>rel</i> ⁺	0.03	0.05
2	+	+	<i>rel</i> ⁺	6.12	0.05
3	+	+	<i>rel</i> ⁻	5.40	0.05
4	—	—	<i>rel</i> ⁺	0.03	2.0
5	—	+	<i>rel</i> ⁺	0.03	3.0
6	—	+	<i>rel</i> ⁻	0.03	0.05
7	+	—	<i>rel</i> ⁻	0.02	0.05
8	—	—	<i>rel</i> ⁻	0.03	0.05

100 μl . *in vitro* protein synthesizing reactions were as described by Zubay *et al.*²⁵. S-30 crude extracts were made from the isogenic pair CP 78 *lac*⁻ *rel*⁺ and CP 79 *lac*⁻ *rel*⁻ containing a deletion of the lactose operon by grinding with alumina. A full complement of amino-acids was 0.22 mM; otherwise all 20 are left out. λ plac_s was used as an exogenous template. β -Galactosidase assays were made with 50 μl . of the reaction mixtures and normalized to OD₄₂₀/20 h, as in Chambers and Zubay³¹ for a 200 μl . reaction mixture. After PEI chromatography and autoradiography the spots were cut out and counted and the amount of MSI and MSII calculated by determining the percentage of the total radioactive phosphate present in these spots.

Table 3 *Rel*⁺ is Dominant to *rel*⁻ *in vitro*

Reaction	413 (<i>rel</i> ⁺) (mg/ml.)	415 (<i>rel</i> ⁻) (mg/ml.)	mmol MS
1	6.5	—	20
2	3.2	—	2
3	3.2	3.2	12
4	1.5	—	0.05
5	1.5	5.0	4
6	0.4	—	0.05
7	0.4	6.1	0.05
8	—	6.5	0.05

100 μl . *in vitro* protein synthesizing reaction mixtures were done as described by Zubay *et al.*²⁵ except that no amino-acids were present in the final reactions. The crude extracts were made from the isogenic pair 413 (*rel*⁺) and 415 (*rel*⁻) as described in Table 2 and mixed as specified. The reactions were incubated for 60 min at 37° C, and the amount of MSI and MSII was quantitated as for Table 2.

In an *in vitro* mixing experiment (Table 3), the *rel*⁺ effect is dominant. MS compounds are synthesized when extracts from stringent and relaxed strains are mixed and incubated without amino-acids. This agrees with the observation that the *rel*⁺ allele is dominant in heterozygotes²⁶.

This difference was observed in three different stringent and relaxed pairs of strains, isogenic except for the *rel* locus

(413 (*rel*⁺) 415 (*rel*⁻) D. Morse; CP 78 (*rel*⁺) CP 79 (*rel*⁻) P. Lengyel; NP 29 (*rel*⁺) NP 290291 (*rel*⁻) F. C. Neidhardt). Fig. 4 shows that the difference between relaxed and stringent strains rests only on the ribosomes. The addition of a high speed supernatant from stringent cells to "relaxed" ribosomes does not stimulate the synthesis of MSI and MSII. Furthermore, the high speed supernatant from relaxed cells does not inhibit synthesis of MS compounds by "stringent" ribosomes.

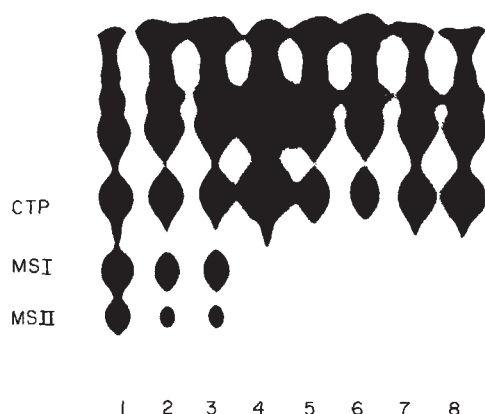


Fig. 4 The high speed supernatant fraction is not needed for the synthesis of MS.

Reaction	Ribosomes		S-100	
	413 (<i>rel</i> ⁺)	415 (<i>rel</i> ⁻)	413 (<i>rel</i> ⁺)	415 (<i>rel</i> ⁻)
1	+	-	-	-
2	+	-	+	-
3	+	-	-	+
4	-	+	-	-
5	-	+	+	-
6	-	+	-	+
7	-	-	+	-
8	-	-	-	+

Reaction conditions as in Table 1. The ribosomes were made from S-30 extracts prepared as described by Zubay *et al.*²⁵ from the isogenic relaxed stringent pair 413 (*rel*⁺), 415 (*rel*⁻) by centrifuging the S-30s in a 'Beckman angle 40' rotor for 2 h at 40,000 r.p.m. at 4° C. The ribosomal pellet was suspended and washed three times with buffer B. The high speed supernatant from the first centrifugation was further centrifuged. After the final wash the ribosomes were suspended in one-eighth the original volume in buffer B and used at a final concentration of 100 µg/ml. The reactions were incubated for 60 min at 37° C.

Discussion

Cashel and Gallant^{5,8} have proposed that during the stringent response a reaction normally involved in protein biosynthesis idles and produces the MS compounds. Our finding that MSI and MSII can be synthesized on the ribosome, and that a factor present in the 0.5 M NH₄Cl ribosomal wash extracted from the stringent but not relaxed strains is necessary for the reaction to occur, supports their hypothesis. The direct involvement of the translocation factor G in the production of the MS compounds suggests that the idling reaction substitutes for the translocation reaction during the stringent response. Because neither supernatant factors nor tRNA are required for the reaction, the signal which triggers the idling reaction may be an unoccupied A site on the ribosome. The A site should remain empty after a translocation event if the appropriate aminoacyl tRNA species is not available. This should be the case following the stimuli which induce the stringent response such as amino-acid starvation or inactivation of an aminoacyl synthetase. If the empty A site is the signal that induces the idling reaction, then the stringent factor may be involved in the recognition of the

empty site or may be required as an essential enzyme, or it may serve both functions. The stringent factor is either the product of the *rel* gene or a protein modified by the action of the *rel* gene.

The possibility that the MS compounds arise as a product of an idling translocation reaction raises the question of whether MSI and MSII are normal intermediates of protein biosynthesis, or arise as the product of a side reaction which occurs only when the appropriate aminoacyl tRNA species are not available. If the MS compounds are an integral part of protein biosynthesis, then the absolute requirement for ATP suggests that ATP may play a heretofore unaccounted role in protein biosynthesis.

The reaction described here may not be the only one in the cell which can synthesize MSI and MSII. Even though relaxed strains do not accumulate MS compounds in response to amino-acid deprivation, they do have normal basal levels of MSI and MSII, and they do accumulate these compounds in response to other changes in cell conditions such as carbon source downshift or deprivation^{27,28} and high salt shock²⁹. This implies that either there is more than one mechanism for MSI and MSII synthesis, or that the one we have described is the only one and relaxed cells are mutated such that, while they do not respond to the signal present during amino-acid starvation, they do respond to other signals and synthesize the MS compounds on the ribosome.

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Interferon inhibits Viral Protein Synthesis in L Cells infected with Vaccinia Virus

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Viral RNA can be detected in L cells pretreated with interferon and infected with vaccinia virus, but protein synthesis ceases as early as 20 min after infection. The effect of interferon must therefore be at the stage of translation rather than transcription.

TREATMENT with interferon renders animal cells resistant to subsequent virus infection. Interferon is not itself directly antiviral but probably causes the synthesis of a cellular protein which acts to inhibit some viral function. Although it is clear that viral replication in cells pretreated with interferon is blocked at an early stage, evidence on the precise site is conflicting (see ref. 1 for a recent review). Evidence has been presented that interferon treatment inhibits virus-specific protein synthesis in cells infected with vaccinia virus², with Mengo virus³ and with Semliki Forest virus⁴. Furthermore, a cell-free protein synthesizing system prepared from interferon-treated cells which displays a diminished ability to translate viral messenger RNA has been described⁵. More recently, however, evidence implying that transcription of the genome may be the primary site of action of interferon has been reported in the cases of vesicular stomatitis virus⁶, vaccinia virus⁷ and SV40⁸.

Early RNA Synthesis

The question of whether interferon inhibits translation or transcription is therefore undecided, especially in the case of vaccinia virus where both types of block have been reported. Here we shall attempt to demonstrate that in L cells which have been pretreated with low doses of purified mouse interferon and then infected with vaccinia virus, the synthesis of viral proteins is inhibited whereas the synthesis of viral RNA is not.

Vaccinia is a large virus with a DNA genome situated in a core structure which is surrounded by an outer envelope (see ref. 9 for a recent review of the structure and function of the poxviruses). Within the core is the virion RNA polymerase. On penetration of the cell the outer envelope is lost, the core is liberated into the cytoplasm, and the polymerase is activated. There follows a burst of viral RNA synthesis which is presumed

to be viral messenger RNA (mRNA). This burst of early mRNA synthesis may be followed by measuring the rate of incorporation of radioactive uridine into cytoplasmic acid-precipitable material (Fig. 1). The maximum rate occurs at

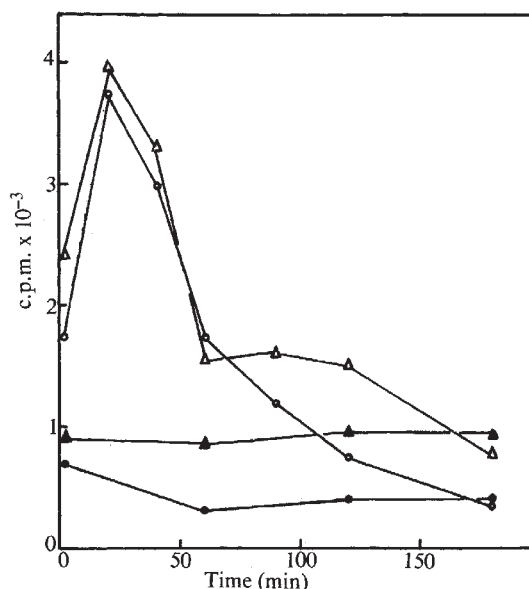


Fig. 1 Rate of RNA synthesis in cells infected with vaccinia virus. Mouse L cells were maintained in suspension culture. Vaccinia virus, strain WR, was grown in HeLa cells and purified essentially according to Joklik²⁰. Cells were infected according to procedure A of Becker and Joklik²¹, at a multiplicity of 500 particles added per cell, for 15 min at 37° C, and then diluted to 1×10^6 cells ml.⁻¹ in Eagle's medium plus 5% calf serum with or without actinomycin D at a final concentration of $1 \mu\text{g ml.}^{-1}$. This was designated zero time. Uninfected cells were subjected to the same procedures with the omission of virus. At specified times, 5-ml. aliquots of cells were removed and labelled with 10 μCi uridine-5-T (30 Ci mmol^{-1}) for 10 min. The cells were chilled to 0° C, washed once with Earle's saline, once with buffer (140 mM NaCl, 10 mM Tris-HCl (pH 7.5), 1.5 mM MgCl_2), resuspended in 2.25 ml. buffer and lysed by the addition of 0.25 ml. 5% 'Nonidet P40'. The nuclei were removed by centrifugation at 800g for 10 min. The top half of the supernatant was decanted and aliquots were precipitated with perchloric acid (final 2%). After 1 h at 0° C, samples were filtered on Whatman glass fibre filters (GF/C), washed with 5 $\times$ 5 ml. 6% trichloroacetic acid, once with ethanol, dried and counted in the scintillation counter. Δ , infected; $\circ$, infected + actinomycin D; $\blacktriangle$, uninfected; $\bullet$, uninfected + actinomycin D.

about 30 min post-infection, a result similar to that obtained in HeLa cells¹⁰. This early RNA synthesis is relatively resistant to moderate doses of actinomycin D ($1 \mu\text{g ml}^{-1}$, Fig. 1). Presumably the drug fails to penetrate the core structure and, although the degree of resistance varies somewhat from one purified virus preparation to another, it is quite feasible to use this dose of actinomycin to suppress cellular RNA synthesis in experiments with vaccinia-infected L cells. The permeability of the core to the drug may depend on the cell-mediated first stage uncoating process since the same strain of virus in HeLa cells appears to be quite sensitive¹¹. The RNA made after 60 min in infected L cells shows substantially greater sensitivity to actinomycin and we infer that this RNA is transcribed from the completely uncoated or newly replicated genome.

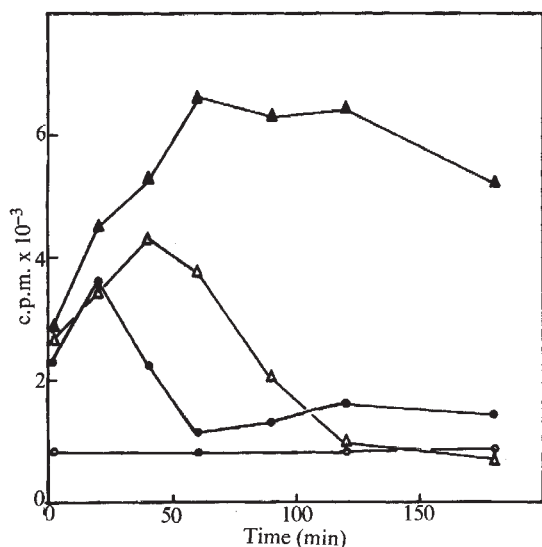


Fig. 2 Effect of cycloheximide on the rate of RNA synthesis in vaccinia-infected L cells. Procedures were as described in Fig. 1, except that cycloheximide was included in the medium where appropriate. ●, Infected cells; △, infected cells plus $0.1 \mu\text{g ml}^{-1}$ cycloheximide; ▲, infected cells plus $1.0 \mu\text{g ml}^{-1}$ cycloheximide; ○, uninfected cells.

Inhibition of protein synthesis stimulates viral RNA synthesis^{10,12}. The effect of very low doses of cycloheximide on viral RNA synthesis is shown in Fig. 2. We have observed similar stimulations with other drugs such as puromycin and pactamycin, and also with amino-acid starvation. The simplest interpretation of these results is that a protein coded by this early mRNA serves to regulate its synthesis. If the formation of this regulatory protein is blocked, then RNA synthesis is prolonged.

If this very early viral RNA is indeed messenger RNA, then one would expect viral proteins to be synthesized within the first hour after infection. We have been able to demonstrate that this is the case by pulse labelling infected cells with ^{35}S -methionine and analysing the pattern of the newly synthesized polypeptides using polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulphate. Autoradiographs of such gels run with uninfected and infected cell extracts at times up to 3 h after infection are shown in Fig. 3. A clear change of pattern in the infected cells compared with the uninfected may be detected as early as 20 min after infection. It seems very probable that the newly synthesized polypeptides are viral in origin although we have not entirely eliminated

the possibility that some of them are cellular proteins whose synthesis is derepressed by infection. The speed with which the pattern changes following infection is striking. Indeed we are not aware of any other animal virus in which the intracellular synthesis of viral proteins occurs so rapidly. We shall describe the features of early protein synthesis in cells infected with vaccinia in detail elsewhere.

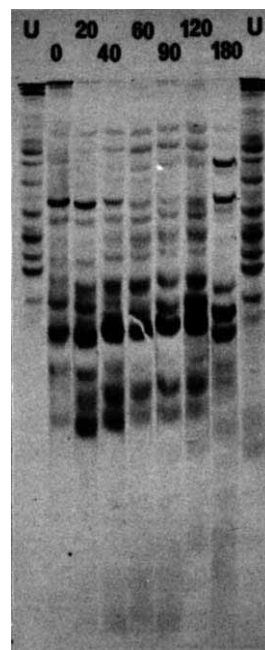


Fig. 3 Polyacrylamide gel analysis of the polypeptides synthesized in vaccinia-infected L cells. Cells were infected as described in Fig. 1. 1.0-ml. aliquots were removed from the cultures at specified times and harvested at 37°C by filtration on glass fibre disks. The cells on the disk were incubated in 1.0 ml. of medium lacking methionine but with the addition of $10 \mu\text{Ci}$ methionine- S^{35} (18 Ci mmol^{-1}). After 20 min at 37°C , the filters were washed with cold buffer containing non-radioactive methionine. The filters were extracted with a mixture of 1.7% sodium dodecyl sulphate, 8 M urea and 0.45 M 2-mercaptoethanol at 100°C for 2 min. The whole of each extract (except for uninfected cell extracts where only half was used) was applied to 10% polyacrylamide gels, electrophoresed, sliced and submitted to autoradiography essentially as described²². These procedures will be described in detail elsewhere. Extracts from uninfected cells are denoted U, and those from infected cells are denoted by the time in min after infection at which the labelling was started. The range of molecular weights of the polypeptides seen in infected cells is between 20 and 120×10^3 . The autoradiograms shown here are relatively under-exposed so that only the principal components are seen (compare Fig. 6).

Effect of Interferon

We have demonstrated that viral RNA synthesis and viral protein synthesis can readily be followed in L cells infected with vaccinia as early as 30 min after infection. We are thus in a position to examine the effect of interferon pretreatment of the cells on these processes. Mouse interferon was kindly contributed by a number of workers. In the work described here we used highly purified material prepared by Dr K. Paucker¹³ (s.a. at least $1.5 \times 10^7 \text{ U mg}^{-1}$ protein), but similar results have been obtained with purified material prepared by Drs E. Knight and R. Z. Lockart¹⁴ and Dr C. Bradish, and also with crude mouse serum interferon.

The effect of interferon pretreatment on the rate of incorporation of radioactive uridine into acid-precipitable material

in the cytoplasm of L cells infected with vaccinia is shown in Fig. 4. Interferon treatment prolongs this incorporation. A dose of 50 U ml.⁻¹ results in a reduction of the yield of virus by 90–95% and is equivalent to about three times the amount required to reduce the yield by 50%. We have determined that interferon pretreatment does not significantly affect the uptake of radioactive uridine into the acid-soluble components of the infected cell during at least the first 2 h after infection. The proportion of the labelled uridine in the form of UTP (determined by thin-layer chromatography¹⁵) and the absolute size of the UTP pool (determined indirectly using unlabelled acid-soluble extracts of infected cells to compete with the incorporation of labelled UTP in the *in vitro* reaction of the vaccinia virion polymerase¹⁶) are also unaltered. We can therefore infer that interferon pretreatment results in a stimulation of cytoplasmic RNA synthesis in vaccinia-infected cells.

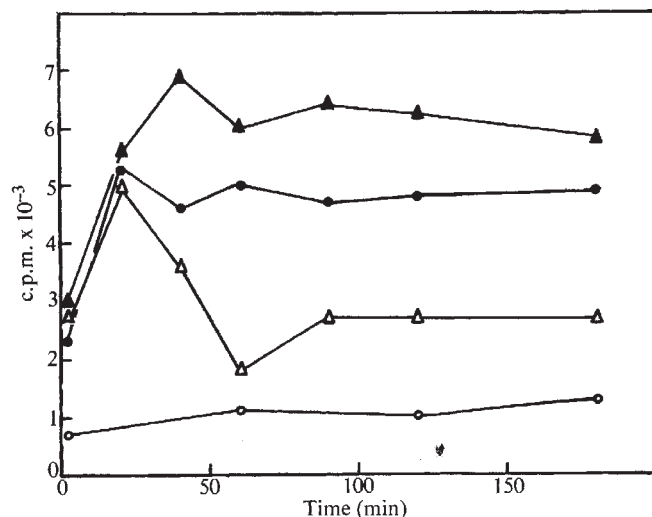


Fig. 4 The effect of interferon pretreatment on the rate of RNA synthesis in vaccinia-infected L cells. L cells at a concentration of 1.5×10^6 ml.⁻¹ in Eagle's medium plus 10% calf serum were treated with highly purified interferon at concentrations of 0, 50 or 120 U ml.⁻¹ at 37° C for 4 h. Cultures were then diluted with an equal volume of medium and stirring was continued for a further 15 h. The cells were harvested and equal numbers of cells were infected as described in Fig. 1, except that dilution after infection was with Tris-buffered Eagle's medium containing 5% calf serum. The use of Tris improves the incorporation of radioactive uridine at later times. Δ , Untreated, infected; $\circ$, 50 U ml.⁻¹, infected; $\blacktriangle$, 120 U ml.⁻¹, infected; $\bullet$, untreated, uninfected. The units of mouse interferon are expressed in terms of the National Institutes of Health Mouse Serum Interferon Interim Reference Reagent (G002-902-026). Approximately 15 such units of mouse interferon were required to reduce the yield of vaccinia virus by 50% in a one-step growth cycle on L cell monolayers.

Evidence that this RNA is indeed viral is presented in Fig. 5, where the sedimentation profiles of the cytoplasmic RNA species synthesized in infected cells in the presence of actinomycin, with and without interferon pretreatment, are compared. There is no significant difference in sedimentation behaviour. The size of the RNA is similar to that reported by others for the material synthesized *in vivo*¹⁷ and *in vitro*¹⁶, and this, together with the insensitivity to actinomycin, strongly suggests that the RNA made in cells treated with interferon is viral. The stimulation of viral RNA synthesis is abolished if the interferon is inactivated by trypsin or by heat, or if it is replaced by purified chick interferon (provided by Dr K. Fantes). This, together with the high purity and low dose

of the mouse interferon employed, strongly suggests that the effects observed are due to interferon and not some impurity.

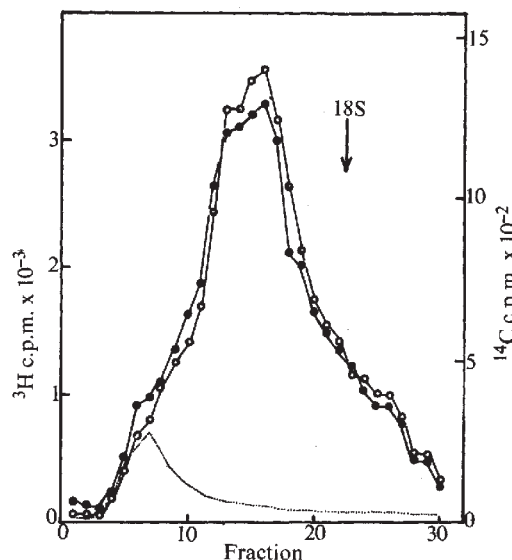


Fig. 5 Sedimentation of the RNA from infected cells. L cells were treated with or without 44 U ml.⁻¹ of interferon as described in Fig. 5, and then infected as described in Fig. 1 except that dilution at zero time was to 2×10^6 cells ml.⁻¹ in medium containing 1 μ g ml.⁻¹ actinomycin D. At 25 min post-infection the interferon-treated cells were labelled with 10 μ Ci uridine-5-T (27 Ci mmol.⁻¹) and the untreated cells with 7.5 μ Ci uridine-2-C14 (55 mCi mmol.⁻¹). At 45 min after infection the cells were collected onto frozen saline, pooled, washed once in cold Earle's saline, once in buffer (10 mM LiCl, 10 mM Tris-HCl (pH 7.5), 1.5 mM MgCl₂), resuspended in 1.0 buffer, allowed to swell for 10 min, homogenized with a Dounce homogenizer and centrifuged at 800g for 5 min. The supernatant was treated with 0.1 vol. 100 mM EDTA and with 0.1 vol. 10% lithium dodecyl sulphate. The sample was layered onto a 5–20% sucrose (w/v) gradient in 100 mM LiCl, 5 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.01% lithium dodecyl sulphate and centrifuged in the SW 41 rotor at 35,000 r.p.m. for 16 h. Fractions were collected (monitoring the absorbance at 260 nm), precipitated with 6% trichloroacetic acid, filtered and washed on glass fibre disks, and counted. Sedimentation is from left to right and the position of 18S ribosomal RNA is indicated. $\circ$, Interferon-treated cells labelled with uridine-5-T; $\bullet$, untreated cells labelled with uridine-2-¹⁴C; . . ., Results of a parallel experiment using uninfected cells (with or without interferon treatment) and run in another gradient.

Stimulation of viral RNA synthesis in interferon-treated cells indicates that transcription is not inhibited and suggests, by analogy with the effect of cycloheximide, that translation is inhibited. We are able to test this directly by examining ³⁵S-methionine-labelled polypeptide synthesis in interferon-treated infected cells. Results from one such experiment are shown in Fig. 6. It is clear that interferon treatment markedly reduces the incorporation of methionine into viral polypeptides as early as 20 min after infection. We have measured the rate of uptake of radioactive methionine and the size of the free methionine pool (using the amino-acid analyser) for infected cells with and without interferon treatment, and find no significant differences. We may conclude therefore that the effect of interferon treatment is to inhibit vaccinia polypeptide synthesis in the infected cell. The small quantities of polypeptides made are viral in origin (this may just be seen in Fig. 6 and is readily observed with longer autoradiographic exposures). The synthesis of cellular proteins is shut off by a component of the infecting virus particle¹¹.

The results of these experiments demonstrate that interferon treatment inhibits the translation of the viral messenger RNA but not its transcription from the vaccinia genome in infected cells and thereby confirm and extend the work of Joklik and Merigan². In particular, we have been able to demonstrate an interferon-mediated inhibition of viral protein synthesis as early as 20 min after infection. This seems to be the earliest time at which an effect due to interferon has been reported.

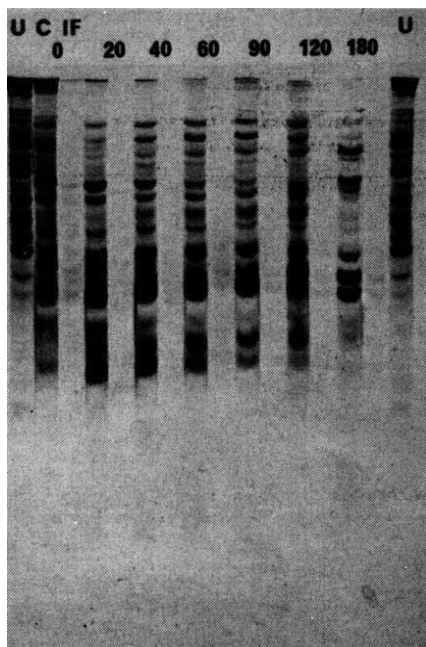


Fig. 6 Polyacrylamide gel analysis of polypeptides synthesized in cells infected with vaccinia and treated with interferon. Cells were treated with 40 U ml.⁻¹ of purified mouse interferon as described in Fig. 4 and then infected and labelled as described in Fig. 3. Pairs of gels are shown for each time point; C denotes untreated infected, IF denotes interferon-treated infected (these are indicated for the 0 min samples only), and U denotes uninfected cells (interferon treatment has no effect on the pattern seen with uninfected cells).

There does occur in L cells which have been infected with vaccinia and treated with interferon a severe cytotoxic effect^{2,18} which, it has been suggested, may in some way be responsible for the stimulation of RNA synthesis^{6,7}. This cytotoxic effect, however, is not observed until 3 or 4 h after infection at the multiplicity of infection that we have used^{2,18}. Electron microscopic examination (performed by Dr J. A. Armstrong) gives no indication of abnormality in interferon-treated cells, compared with untreated, until 3 h after infection. Furthermore, we have found that in chick cells, in which no cytotoxic effect is observed¹⁹, the effect of interferon treatment on vaccinia RNA and protein synthesis is very similar to that found in L cells (in preparation). It is therefore improbable that the cytotoxic effect is the cause of the very early inhibition of protein synthesis that we observe.

There have been reports that viral RNA synthesis is inhibited in interferon-treated cells infected with a number of viruses⁶⁻⁸. These results seem to be at variance with our own, and there are two possible explanations for the discrepancy. First, the interferon mechanism may inhibit more than one type of viral function, transcription as well as translation, for example^{6,7}, and the effects observed depend on the experimental system employed. The observations of Jungwirth *et al.*¹⁹ could be consistent with this notion. They found that while there was a stimulation of RNA synthesis in interferon-treated vaccinia-

infected L cells, in interferon-treated chick cells infected with the closely related cowpox virus, less RNA was made. Since in this latter case, however, cycloheximide treatment also resulted in inhibition of viral RNA synthesis it was considered that differences in the interferon effect in the two systems reflected differences in the mechanism for control of RNA synthesis rather than in the mechanism of interferon action.

The second type of explanation is that alternative interpretations of at least some of the conflicting data may be made. In our work we have paid especial attention to a number of points. We have confirmed that the incorporation of exogenous uridine and methionine into acid-precipitable material are proper measures of RNA and protein synthesis, respectively. We have used interferon preparations from different laboratories, including some with what appear to be the highest reported specific activities. We have been able to demonstrate a substantial inhibition of viral protein synthesis but no inhibition of viral mRNA synthesis with low, and what one hopes are physiological, doses of interferon. It would be interesting to know the effect of low doses of highly purified interferon on protein synthesis in these other virus-cell systems^{6,7}.

The occurrence of viral messenger RNA production together with the inhibition of viral protein synthesis implies a block at some stage in the processing of the RNA, between the site of its formation in the vaccinia core structure and the site of its function in the polysomes. Elsewhere we shall show that both the initiation events of viral polypeptide synthesis and the elongation of the growing polypeptide chain are inhibited in interferon-treated cells. Furthermore, it has been possible to prepare a cell-free protein synthesizing system which shows a substantial and reversible interferon-mediated inhibition²³.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Circular Polarization of Twilight

LINEAR polarization of clear daytime sky and twilight is produced by molecular (Rayleigh) scattering and aerosol (Mie) scattering, which predominates in the infrared. Incident linearly polarized light scattered by aerosols is in general elliptically polarized, whereas no ellipticity can arise from the molecular component¹. The principal component of clear daytime sky arises from single scattering of unpolarized sunlight and is not elliptically polarized. However, whenever multiple scattering by the aerosol component is important, the strong linear polarization produced on the first scattering will lead to elliptical polarization from the second and subsequent scatterings. Although in the daytime sky this mechanism should give only a small ellipticity² (10^{-5} – 10^{-3}) the possibility of a substantially larger effect at twilight arises because there is no direct illumination. We report here observations of circular polarization of twilight of order 10^{-3} .

The observations were made with a polarimeter^{3,4} which uses an electronically switched Pockels cell operated as a reversible quarter-wave plate to convert circular into linear polarization, which is then analysed by a Wollaston prism followed by two 'RCA C31034' gallium-arsenide photomultipliers. The wide spectral response of these tubes allowed measurements to be made in two well-separated wavelength bands: an infrared band from 7800–8800 Å (half-power points), defined by a 'Schott RG 780' filter, and an ultraviolet band from 3500–4000 Å, isolated by a 'Corning 4-96' and a 'Corning 7-54' filter. Since a very small component of circular polarization is to be measured (~ 0.001) it is important to eliminate completely the instrumental effects, primarily due to imperfections in the Pockels cell, which cause linearly polarized light to appear slightly elliptical. This is achieved by rotating the instrument through exactly 90° ; the spurious signal from the linear polarization is reversed while the true circular component is unaffected.

The initial observation of twilight circular polarization was of dawn light in the infrared made at the 82-inch Struve reflector of McDonald Observatory in February 1972. Since it was possible that the telescope optics were introducing the small ellipticity detected (~ 0.002), further measurements were made with the instrument viewing the sky directly with a baffled tube attached to define an f-13 beam. The data given below were obtained at the Rutherford Observatory in Manhattan during a period of very clear weather. All observations were made along a line of sight due south at an elevation of 45° . For each datum point, the mean of a pair of measurements taken before and after rotation, a total of $N(\sim 4 \times 10^7)$ photoelectrons was detected. The error in the normalized Stokes parameter V/I due to counting statistics is then $1/\sqrt{N} \approx 0.016\%$. Apertures of different diameter were used to keep the counting rate below 1 MHz, when dead time correction can be neglected.

In Fig. 1 the circular polarization measured in the infrared band before dawn and after sunset is plotted as a function of time and angle of the Sun below the horizon. The vertical error bars plotted show the standard deviation calculated from counting statistics. An altitude of 0° is assigned at sunset given by the American Ephemeris, that is, when the upper limb is apparently on the horizon. The infrared measurements were obtained at dusk on March 26 and 28, and at dawn on

March 28. Observations in the ultraviolet band were made on March 27 at dusk. In the ultraviolet no significant circular polarization was detected at any angle. The mean value when the Sun was between 3° and 6° below the horizon was -0.03% .

It is seen from Fig. 1 that when the Sun is 3° or more below the horizon, there is a definite component of circular polarization in the infrared. This increases to about 0.2% when the Sun is 7° below the horizon, when the twilight becomes too faint to measure. When the Sun is within 2° of the horizon, the effect, if present at all, is much weaker, $V \leq 0.03\%$.

All the qualitative features of the observed circular polarization are in accordance with the expected effects of scattering in the atmosphere. Because the instrument is pointed due south, the scattering geometry at dusk and dawn is unchanged except for the handedness or parity. Thus the magnitude of circular polarization at a given angle of the Sun below the horizon should be the same at dusk and dawn, while the sign should be reversed. The data in Fig. 1 confirm that the sense of polarization does reverse and the magnitude has roughly the same dependence on the Sun's altitude. It should be noted that the linear polarization in the observed direction is essentially the same during all the measurements. Thus the possibility of the measured circular polarization being induced in some unknown way by the strong linear polarization can be ruled out.

The increase of polarization with increasing angle of the Sun below the horizon is expected, as the geometry of the multiple scattering becomes more favourable for the production of circular polarization and as single scattering is removed. For example, there will be essentially no contribution from single scattering when the Sun is 4° below the horizon, because the shadow of the horizon is then 10 miles high.

The circular polarization in the ultraviolet is weak and, if present at all, is an order of magnitude less than that in the infrared band. This is expected because in this wavelength band Rayleigh scattering, which does not produce elliptical polarization, is predominant because of the λ^{-4} dependence. The contributions to the Earth's albedo from Rayleigh and aerosol scattering estimated by Hansen⁵ are in the ratio 4 : 1 in the ultraviolet band (3750 Å) and 1 : 3 in the infrared band.

Unfortunately, quantitative models of the scattering and polarization at twilight are not simple to construct, and it is unlikely that twilight observations can be used to obtain useful data about the scattering particles. Elliptical polarization produced by scattering in the air of artificial sources of linearly

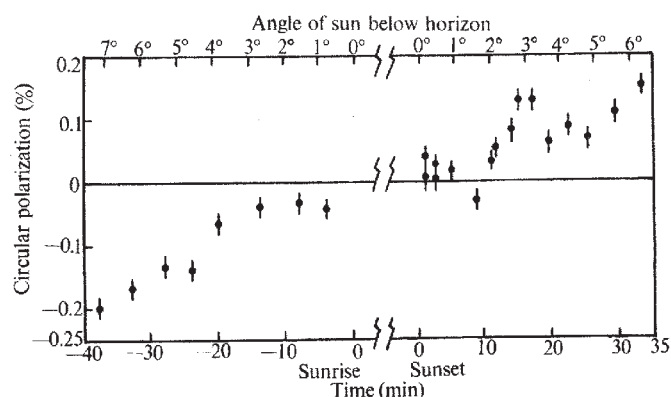


Fig. 1 Circular polarization of the twilight sky measured in a wavelength band from 7800–8800 Å.

polarized light^{6,7} is more useful for this purpose. The discovery of a definite natural circular polarization at twilight does suggest, however, that, with increased precision, measurements of the predicted small daylight component are possible. These could give useful information about particles in the atmosphere and be valuable in studies of meteorology and air pollution.

In conclusion, we note that the circular polarization recently observed in some astronomical objects is also thought to be due to Mie scattering. The planets Jupiter and Venus have a measured circular polarization⁸ of order 10^{-4} , and this is interpreted by Hansen² in terms of multiple scattering in reflecting clouds. Gehrels⁹ reports circular polarization of 0.4% in the infrared of VY CMa which is a star surrounded by a small bright reflexion nebula. Here the details of the mechanism are not so certain, and either reflexion or birefringence caused by aligned grains may be involved¹⁰.

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Magnetic Anomalies on the Reykjanes Ridge

THE symmetrical magnetic anomaly pattern¹ over the axis of the Reykjanes Ridge has been interpreted^{2,3} as evincing sea-floor spreading during the past 10 m.y., and Talwani *et al.*⁴ have used magnetic survey data of the Reykjanes Ridge to revise the reversal time scale for the past 10 m.y. They were also able to show that the magnetization of basement within the axial anomaly is 0.03 emu, three times greater than the value assigned to the magnetization of basement underlying the flank anomalies, 0.01 emu.

Two important problems concerning the magnetic anomalies on the Reykjanes Ridge remain to be answered. First, does a hiatus in spreading coincide with the discontinuity in the sediment cover just beyond the position of anomaly 5 (ref. 4)? Second, what are the details of the spreading pattern over the flanks of the Reykjanes Ridge, beyond anomaly 5, and do the proposed⁵ extinct axes exist on the flanks? The latter question is especially important because a reliable identification of the anomaly pattern generated during the past 45 to 50 m.y. in this area can provide a check on the anomaly identifications

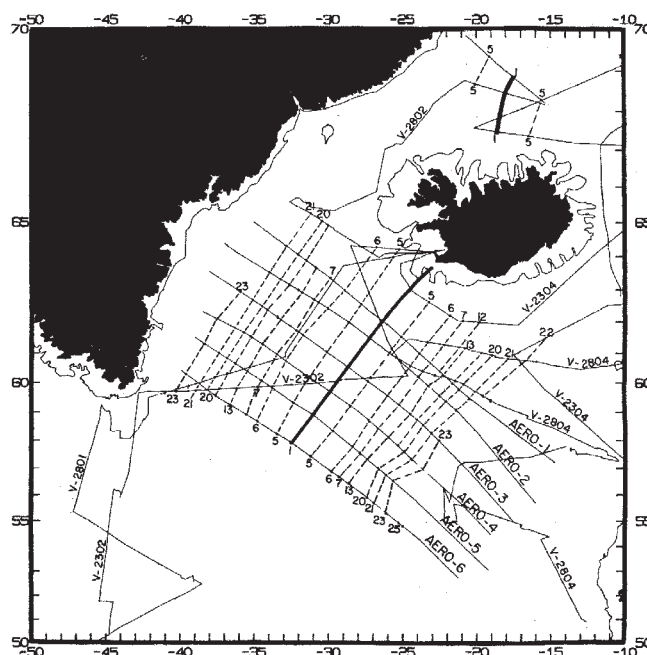


Fig. 1 Tracks of the RV Vema and flight lines from Godby *et al.*⁵ are shown on a mercator projection. Magnetic anomalies identified on the various tracks have been correlated from track to track and are shown by the dotted lines for all but the axial anomaly, which is marked by the heavy solid line.

proposed for the North Atlantic between the Azores–Gibraltar Ridge and the Charlie fracture zone. Prior to 50 m.y. BP, spreading on the Reykjanes Ridge cannot be directly compared with that on the Mid-Atlantic Ridge between the Azores–Gibraltar Ridge and the Charlie fracture zone at 52° N because the spreading centre in the Labrador Sea⁶ was active and the Reykjanes Ridge defined the Eurasian–Greenland plate boundary, and not, as at present, the Eurasian–North American plate boundary. Magnetic lineations 47–60 m.y. old on the flanks of the Reykjanes Ridge have been identified by Vogt⁷.

Vogt *et al.*⁸ summarized results of a detailed but unpublished magnetic survey between the Reykjanes Ridge and Rockall Bank. They state that spreading was very slow during the period between 42 and 18 m.y., and that during this slow spreading period fracture zones spaced 100 km apart developed. Parallel to each of these fracture zones they describe a “broad, parallel band, of the order of 30 km wide, devoid of linear magnetic anomalies”. These results have been quoted from the abstract⁹ of an unpublished paper. Neither the anomaly identifications nor the absence of identifiable anomalies in the 30 km wide band have been shown in the published literature.

Fig. 1 shows the tracks of Vema cruises 23 and 28 together with the flight lines from the aeromagnetic survey of Godby *et al.*⁵. Vema used satellite navigation with an accuracy of a fraction of a mile. Godby *et al.*⁵ used Loran A, doppler and astronomical fixes. No discrepancies in anomaly location appear in the few locations where Vema tracks and the flight lines intersect. Detailed survey tracks of the Vema over the crest of the Reykjanes Ridge were reported by Talwani *et al.*⁴ and are not shown in this paper. Magnetic lineations are also presented in Fig. 1. The identifications within the nomenclature system of Heirtzler *et al.*¹⁰ are new for the anomalies beyond number 5, and are based on comparison of the data with computed models. Large offsets and/or closely spaced fracture zones are not suggested by the linear trend of the anomalies, and there is no area where anomalies cannot be identified. The relatively constant trend of the lineations does not, however, preclude the existence of fracture zones, provided that the displacement across them is very small.

Fig. 2 presents the projected Vema data, the aeromagnetic data published by Godby *et al.*⁵ and a theoretical model.

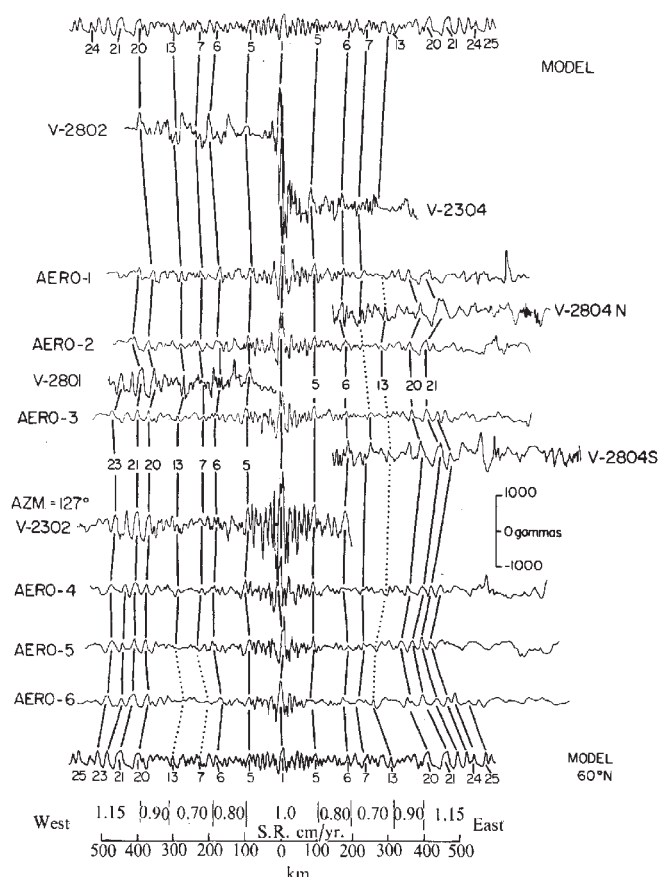


Fig. 2 Magnetic data along the tracks shown in Fig. 1 have been projected perpendicular to the trend of the Reykjanes Ridge. Aeromagnetic data, identified as AERO 1 through 6, have not been projected because the flight lines trend roughly perpendicular to the ridge. Anomalies have been correlated with the preferred theoretical model generated for 60° N latitude. Dotted lines have been used where the anomaly identification is tenuous; better correlations have been noted by the solid connecting lines between the tracks.

The Vema data were projected perpendicular to the 037° azimuth of the Reykjanes Ridge axis. The azimuth of the flight lines of Godby *et al.*⁵ is roughly perpendicular to the Ridge trend, and these data were taken directly from their publication. Several models were computed to check the anomaly identification because the character of anomalies between numbers 5 and 19 changes rapidly at spreading rates less than 1.5 cm yr⁻¹. Only the model which best fits the data is shown here, and, considering the relatively slow spreading rates, fits the data extremely well. Magnetic anomalies can be traced from track to track quite easily, and sufficient character is preserved on all the profiles to permit a confident identification of "key" anomalies 5, 6, 7, 13 and 20, and 21. The slow spreading rates have produced a blending of the series of anomalies between numbers 5 and 6, 6 and 7, and 13 and 18, so that on both the observed and on the theoretical model, these series of short period events tend to merge into single broad positive anomalies.

The spreading rates used in the model shown in Fig. 2 decrease to a minimum of 0.7 cm yr⁻¹ between 21.5 and 38.5 m.y. The rates for other times since 47.5 m.y. are nearly the same, however: 1.0 cm yr⁻¹ between 0 and 10 m.y.; 0.8 cm yr⁻¹ between 10 and 21.5 m.y., and 0.9 cm yr⁻¹ between 38 and 47.5 m.y. Therefore, we can state that since 47.5 m.y., there is no evidence of a major slowdown in the rate of spreading on the Reykjanes Ridge. In particular, there is no evidence in support of a near hiatus of spreading just prior to anomaly 5 time (10 m.y.), coincident with the sediment discontinuity noted by Talwani *et al.*⁴. Nor is there evidence supporting

the extinct ridge axes on each flank of the Reykjanes Ridge as outlined by Godby *et al.*⁵.

It is generally accepted that the Reykjanes Ridge and the Mid-Atlantic Ridge north of the Azores-Gibraltar Ridge have delineated the Eurasian-North American plate boundary since the cessation of spreading on the Labrador Ridge 45-50 m.y. ago⁶.

The pattern of spreading rates since 45 to 50 m.y. ago on the Reykjanes Ridge can therefore be compared with those proposed for the North Atlantic. By contrast with the comparatively well developed magnetic anomalies associated with the Reykjanes Ridge, those generated during the past 47.5 m.y. on the Mid-Atlantic Ridge north of the Azores-Gibraltar Ridge are extremely poorly developed, and consequently various different anomaly identifications have been proposed. Two identifications in the North Atlantic have been proposed by Pitman *et al.*¹¹ and by Williams and McKenzie¹². These models are essentially similar except for the identification of anomaly 13. In the Pitman *et al.* model this anomaly occurs much closer to the ridge axis than it does on the Williams and McKenzie model. As a consequence, Pitman *et al.* had to suggest that spreading in the North Atlantic almost ceased between 10 and 38 m.y. ago. In contrast, the model proposed by Williams and McKenzie¹² and adopted by Pitman and Talwani¹³ allows a relatively constant spreading rate during this period. Because anomaly 13 is so poorly developed in the North Atlantic, neither of these models can be accepted with confidence on their own merits. The relatively constant pattern of spreading rates observed on the Reykjanes Ridge does, however, lend support to the identification of anomaly 13 proposed by Williams and McKenzie¹².

Fig. 3 demonstrates the similarity between the pattern of opening observed on the Reykjanes Ridge with the pattern of opening outlined in the two basic models proposed for the North Atlantic. Because the Reykjanes Ridge trends obliquely to the Charlie fracture zone at 52° N (the Ridge trend is 037° and the fracture zone trends 095°¹⁴ making the angle between the Ridge and the fracture zone only 58°), the data from the Reykjanes Ridge as measured along a line perpendicular to the azimuth of the Ridge have been corrected to give the true rate of opening in the direction parallel to the Charlie fracture zone. Fig. 3 shows that the pattern of opening proposed by Williams and McKenzie¹² parallels closely the pattern of opening on the Reykjanes Ridge. The pattern proposed by

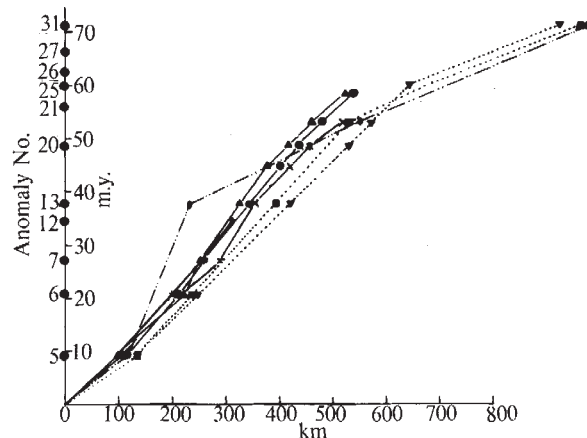


Fig. 3 Observed data from the Reykjanes Ridge have been corrected to give the distance from the ridge axis parallel to the direction of opening of the Eurasian-North American plates. The corrected distances to various anomalies have been plotted against anomaly age together with the corresponding distances to the same anomalies as proposed by the spreading rate models of Pitman *et al.*¹¹ and Williams and McKenzie¹². Data from the North Atlantic can be compared with those from the Reykjanes Ridge only for the past 47.5 m.y. ●, Pitman *et al.*¹¹; ▼, Williams and McKenzie¹²; ■, Pitman and Talwani¹³; ▲, 2801; ●, 2302; +, 2304; x, 2804.

Pitman *et al.*¹¹ is possible only if the pole of opening during the interval 10–38 m.y. (between anomaly 5 time and anomaly 13 time) was located south of the Azores–Gibraltar Ridge. This not only implies a large shift of the pole of opening (the pole lies north of the Reykjanes Ridge both prior to 38 m.y. as well as subsequent to 10 m.y.), it also requires that the spreading rates during the interval 10–38 m.y. increase rapidly northwards of the Reykjanes Ridge. Talwani and Eldholm¹⁵, however, find no evidence for such an increased rate on the Mohn's Ridge in the Norwegian Sea where the magnetic anomaly pattern is well developed.

These new marine and previously published aeromagnetic data across the Reykjanes Ridge outline a pattern of relatively constant spreading rates for the past 47.5 m.y. The anomaly pattern is surprisingly well developed and can be identified with some confidence, in marked contrast to the poor quality of anomalies found south of 52° N in the Atlantic. Because the Reykjanes and the Mid-Atlantic Ridges have defined the North American–Eurasian Plate boundary during this period, the spreading rate pattern observed on the Reykjanes Ridge can be used as a control on anomaly identifications in the North Atlantic. In particular, the Reykjanes Ridge data provide support for the identification of anomaly 13 made by Williams and McKenzie¹² and do not support the identification of this anomaly by Pitman *et al.*¹¹, which demands a near hiatus in the spreading between anomalies 5 and 13.

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Origin of Deep Sea Cherts in the North Atlantic

SEISMIC profiling has revealed two strongly reflecting layers beneath the floor of the North Atlantic¹. The shallower reflector is referred to as "horizon A" and the deeper as "horizon B"; JOIDES drill cores from the eastern and western North Atlantic and the Caribbean show that horizon A consists of a cherty material of Late–Early Eocene to Middle Eocene age^{2–4}. Although the material of these layers is usually described as

chert, the mineralogy is variable and the Eocene and Upper Cretaceous layers are composed chiefly of cristobalite rather than quartz, so they are not true cherts⁵.

It has been suggested that these layers were formed as a result of volcanic activity on land; alteration products of terrestrial pyroclastics carried by winds and sea currents would have augmented the SiO₂ content of seawater, increasing the production of siliceous plankton and enhancing the preservation of their skeletons. This would have led to the deposition of cherty beds^{6,7}.

In my view, however, although terrestrial volcanism may account for small areas of silica-rich sediments, it cannot explain the widespread horizon A throughout the North Atlantic and Pacific basins.

Dietz and Holden⁸ and Berggren and Phillips⁹ have independently suggested that the opening of the Norwegian Sea during the Eocene would have increased the circulation and productivity of surface water and would have led to the deposition of radiolarian and diatom-bearing sediments. Here I propose an alternative hypothesis; that horizon A—and earlier chert beds which may be present—were deposited when periods of seafloor spreading (break-up of continents) coincided with periods of global temperature zonation.

The model invokes episodic seafloor spreading^{10–12}, and I propose the following sequence of events. (i) Submarine volcanic emanations are preceded by basaltic eruptions along newly formed oceanic fissures. (ii) Silica is leached by deuteric alteration of lavas and released to seawater. The water, particularly at the water/sediment interface, becomes enriched in SiO₂ inhibiting dissolution and ensuring preservation of siliceous tests on the seafloor. (iii) Proliferation and evolutionary diversification of oceanic plankton including diatoms, radiolarians and silicoflagellates, also related to seafloor spreading and break-up of continents¹³, may have contributed indirectly to deposition of cherty beds on the seafloor.

Geological evidence suggests that periods of uniform climates were interspersed with intervals characterized by marked latitudinal temperature zonation. During equable global climates, high latitude air and seawater temperatures would have values close to those prevailing in equatorial regions; deep water which today is formed principally by sinking of cold, dense water would be reduced. Horizontal and vertical oceanic circulation would diminish and the plankton productivity of surface water would be low. Conversely, during intervals characterized by latitudinal thermal gradients such as prevailed during the Quaternary, cold water formed in the polar seas. As this cold, dense water sank, it was replaced by upward movement of lighter, nutrient-rich water. Because ocean fertility depends principally upon the availability of inorganic plant nutrients, production of silica secreting phyto- and zooplankton must have been considerably enhanced throughout these periods.

Deposition of horizon A coincided with the opening of the Norwegian Sea and with the Eocene cooling (ref. 14 and Fig. 1). Separation of Greenland from Eurasia by rifting and magma intrusions along newly formed fissures marked the commencement of spreading over a large segment of ocean floor. Outpouring of vast volumes of magma during early stages of basin formation coincided with invasion of the Atlantic by polar water and with a cool climatic period¹⁴. The factors described above made more SiO₂ available, increased vertical and horizontal water circulation, and thus enhanced the rates of production of siliceous plankton and their subsequent preservation and accumulation on the seafloor.

Several cycles of chert deposition may have occurred in the life-span of the ocean: each cycle is thought to commence when active seafloor spreading (break-up of continents) accompanied by submarine volcanism coincided with periods of global temperature zonation and consequent vigorous vertical and horizontal water circulation.

The model proposed for the deposition of layer A may be valid for the formation of earlier cherts. The opening of the South Atlantic Ocean about 130 m.y. BP^{4,8,9} by rifting,

followed by submarine volcanic emanations and injection of large volumes of lava along the Mid-Atlantic Ridge, and by deuteritic weathering of the latter, also coincided with a cool climatic episode (refs. 15 and 16 and Fig. 1). This newly formed waterway initiated strong currents in the Atlantic transporting cold silica rich deep water to the North Atlantic. Intensified circulation associated with global thermal gradients stimulated productivity of the overlying water. Conditions during the Early Cretaceous appear similar to those prevailing in Late-Early to Middle Eocene time, and hence are suitable for deposition of cherts over vast areas of the seafloor.

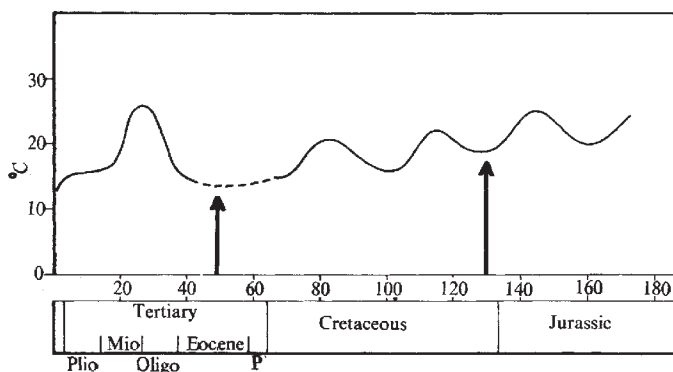


Fig. 1 Generalized palaeotemperature curve for Mesozoic and Cainozoic high latitude seas, based on oxygen isotope determinations (after Dorman)¹⁶. Vertical arrows represent times of separation of continents and initiation of vigorous oceanic circulation. The left hand arrow represents the time of deposition of horizon A; the right hand arrow may correspond to the deposition of an earlier cherty bed.

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Oxygen Isotope Evidence for Bottom Freezing on the Amery Ice Shelf

A SUBSTANTIAL outflow of ice from the Antarctic Ice Cap is via the floating ice shelves¹. It is therefore important in establishing a mass budget for the continent as a whole to have some measure of the budgets of the ice shelves. Calculations using continuity and isostatics in conjunction with measured velocities and strains can give the mass flow, but errors in measurement and the great difficulty in allowing for any state of imbalance in the shelf mass equilibrium make the total amount of water lost or gained by the shelf while it is in contact with the sea uncertain². The measurements presented here, by showing the total thickness of such ice on sea water, give an integrated value of the freezing rate as the shelf moves out.

During the 1968 Australian National Antarctic Research Expedition (ANARE) to the Amery Ice Shelf a borehole 315 m deep was drilled in the shelf at the point marked G1 (Fig. 1). The ice core obtained has been analysed for variations in the ratio of the isotopes of oxygen ¹⁸O and ¹⁶O expressed as $\delta^{18}\text{O}$ relative to standard mean ocean water (SMOW)³. This fractionation of ¹⁸O/¹⁶O in precipitation is a complicated function of meteorological processes whereby the water from the oceans is evaporated, transported by atmospheric circulation and condensed to snow or rain. The most important variable is the temperature of the final condensation process; hence over an area which is subject to the same principal atmospheric flow the isotope ratio averaged over several years can be related quite closely to mean annual temperature^{4,5}.

The $\delta^{18}\text{O}$ profile at G1 (Fig. 2a) suggests that the shelf consists of ice from three distinct sources. The uppermost layers from 0 to 70 m deep have $\delta^{18}\text{O}$ values from -19‰ to -23‰ . These values are typical of snows deposited at low elevations near the coast of Antarctica⁶ and it is assumed that this ice was laid down by precipitation on to the ice shelf itself.

The second section from 70 to 270 m appears to be ice which has flowed from the Lambert Glacier drainage basin where the lower mean annual temperature ($\sim -30^\circ\text{C}$) increases the de-

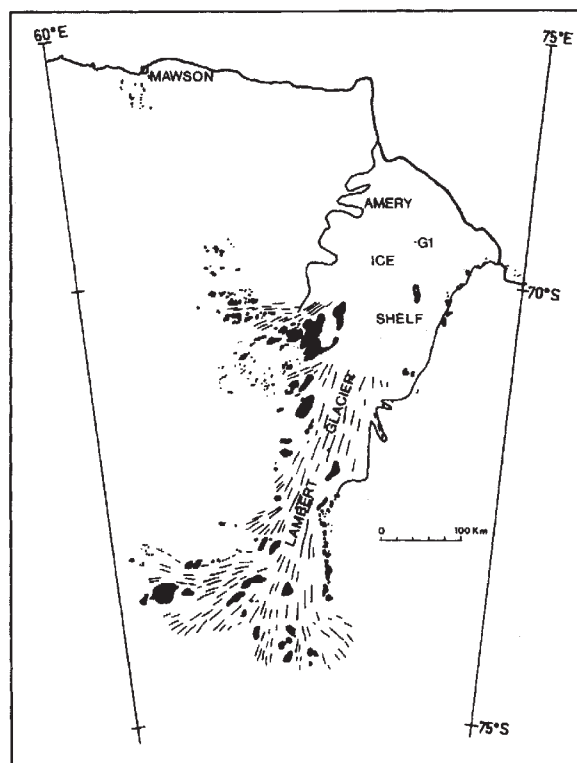


Fig. 1 Amery Ice Shelf showing the position of the borehole (G1) and lines of principal ice flow in the Lambert Glacier.

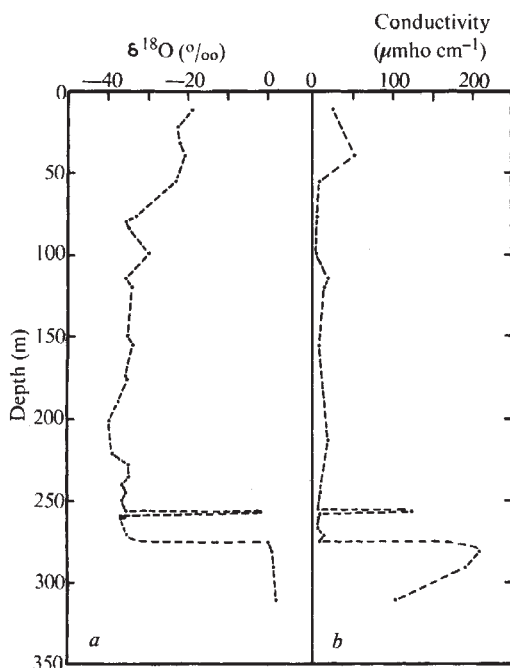


Fig. 2 Oxygen isotope (a) and electrical conductivity (b) profiles to a depth of 315 m at location G1 in the ice shelf.

pletion of ^{18}O . A fairly distinct transition might be expected between the two sections as there is between the glacier drainage basin and the floating ice shelf, a region of very little net accumulation of snow but with considerable elevation (and temperature) change⁷.

The very sharp change in the isotope values at 270 m appears to mark the bottom of the glacier ice; below this depth the ice is assumed to be frozen on sea water. Values of $\delta^{18}\text{O}$ for this ice are close to that of ocean water (around 0‰, the slightly positive values resulting from fractionation occurring in the slow freezing process. (H_2^{18}O is more easily frozen so its concentration is enhanced.)

These deductions are confirmed by electrical conductivity measurements on melted core samples (Fig. 2b) which show low conductivities (< 50 mho) for the glacier and upper shelf ice but about 100 times higher after the transition. The conductivity then decreases towards the bottom presumably owing to the decreasing rate of freezing as the shelf moves out allowing more complete removal of the salt. This slowing of the freezing rate is also shown by the increasing fractionation of the oxygen isotopes.

The thickness of the shelf at G1 has been determined by ice radar to be 428 m. Isostatic calculations using the measured density profile give a thickness of 466 m; however, irregularities in the surface slope indicate that the shelf is grounded, and hence raised, near G1. A lifting of 4 m would account for the thickness discrepancy.

Using measured velocities and distances⁷ and a total thickness of 428 m an average bottom freezing rate of 30 cm yr⁻¹ is calculated to accumulate the 158 m of sea water ice. Preliminary examination of the temperature profile in the G1 borehole suggests that such a rate of basal accumulation is quite possible.

An alternative explanation of the sea water ice is that it is a localized feature at G1, possibly a crevasse which has opened in the shelf bottom letting in water which has then frozen. We consider this unlikely, because the flow of the ice would tilt such a crevasse producing only a narrow layer of salt ice. We suggest that the layer at 256 m was produced in this way, and its proximity to the base of the glacier ice indicates that the break occurred near the point where the ice starts floating; that is where tidal stresses are greatest and most likely to cause crevassing. A total thickness of glacier ice of 410 m would, with the measured strain rates, require the shelf to be in a state

of considerable imbalance. If balance conditions are assumed the accreted water is necessary to give the correct total thickness.

A paper showing in detail the ice shelf structure and strain rates together with comparisons of isotope ratios in the ice shelf core with those in shallow cores in the Lambert Glacier will be published at a later date.

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Globorotalia truncatulinoides: a Palaeo-oceanographic Indicator

STUDIES of living planktonic foraminifers have established that many species have limited tolerance to changes in temperature and salinity; they are adapted to various water depths and their distribution on the seafloor usually resembles that in the water layers above. Planktonic foraminifers are therefore useful in reconstructing the history of oceans and seas, and here I describe the distribution of *Globorotalia truncatulinoides* and associated fauna in the North Atlantic and Mediterranean, demonstrating their potential value as tracers of palaeocurrents and specific water masses.

At present the sinistrally and dextrally coiled forms of *G. truncatulinoides* live in different water masses and have distinct depth habitats. Sinistral populations predominate in the warm Gulf Stream, the North Atlantic Current and its branches, and in the Northern Sargasso Sea, whereas dextral forms inhabit the deep and colder water of the Equatorial Atlantic. Both varieties have peak abundances during winter months¹⁻³.

Ericson *et al.*⁴ have charted the distribution of *G. truncatulinoides* in North Atlantic surface sediments and recognize three provinces: a left coiling one, in mid latitudes, and two right coiling provinces, one in the equatorial-subtropical latitudes and another in the North-east Atlantic (Fig. 1). According to Mann⁵ the Gulf Stream proper, which flows north from Cape Hatteras along the eastern North American coast, divides in the vicinity of 40° N and 45° W, continuing under the name of "North Atlantic Current". One arm of the current bends north-west, while the main branch continues essentially east, south-east and north-east. Part of the east-flowing current enters the Mediterranean at surface (ref. 6 and Fig. 1). The distribution of *G. truncatulinoides* in surface Atlantic sediments⁴ (Fig. 1) suggests strongly that the branching of the North Atlantic Current is recorded by the two forms of *G. truncatulinoides*: the sinistral variety is carried by the warm currents north-west as well as east and penetrates the Mediterranean⁷⁻¹¹ (Fig. 1) and the right coiling variety inhabits the colder North-east Atlantic water mass.

The vertical distribution of planktonic foraminifers in sediment cores taken beneath the North Atlantic Current near Gibraltar indicates that in postglacial sediments predominantly sinistral *G. truncatulinoides* are associated with other warm-temperate North Atlantic Current faunal elements. This population replaced colder planktonic foraminifers roughly 11-13,000 years ago^{12,13}. During the last glaciation, dextral

G. truncatulinoides, together with other cold-tolerant species such as *Globigerina bulloides*, *Globorotalia inflata*, *Globigerina pachyderma*, *Globigerina quinqueloba*, *Globorotalia scitula*, and *Globigerinita glutinata*, inhabited the Gibraltar sector of the Atlantic¹². These taxa are found in postglacial Labrador and Norwegian Sea sediments^{14,15}.

The faunal data suggest that fluctuations in past climates have influenced oceanic circulation: during the last glacial (Wisconsin, Würm) the Gulf Stream and the North Atlantic Current migrated south by several degrees. This migration resulted in the replacement of warm-temperate planktonic faunas by northern immigrants in the Gibraltar sector of the ocean and in the Mediterranean. These taxa now inhabit the cold Atlantic water masses north of the Gulf Stream and the North Atlantic Current.

Micropalaeontological analyses of sediment cores from the Mediterranean allow the reconstruction of the climatic and hydrological history of this sea back through the last interglacial. Two cores for which absolute ages, micropalaeontological data and ¹⁸O/¹⁶O determinations are available illustrate these oscillations⁸⁻¹¹ (Fig. 2).

Variations in coiling direction of *G. truncatulinoides* reflect changes in surface water temperatures also inferred from other planktonic foraminifers and oxygen isotope determinations. In postglacial sediments sinistral *G. truncatulinoides* occur together with *Globigerinoides ruber*, *Globigerinoides sacculifer*, *Globigerinella aequilateralis*, *G. inflata*, and *G. bulloides*. During the last glacial, the Mediterranean supported colder water elements, including dextral *G. truncatulinoides*, *G. bulloides*, *G. scitula*, and *G. inflata*.

Radiometric age determinations^{8-12,16}, coupled with close interval inter- and intra-basinal biostratigraphic correlations between cores, indicate that during the late Cainozoic, climatic oscillations in the Mediterranean were contemporaneous with those in the Atlantic.

The fauna of the Mediterranean and Atlantic have close affinities except during periods of stagnation (Fig. 2) when the Mediterranean planktonic population was dominated by euryhaline and low salinity-tolerant species, such as *G. ruber*, *Globobulimina dutertrei* and *G. quinqueloba*.

Several taxa living in the Atlantic did not penetrate the Mediterranean. This may be because of the shallow Gibraltar sill depth, the depth habitat of certain species and/or the higher salinities of the Mediterranean which may inhibit the survival of stenohaline taxa.

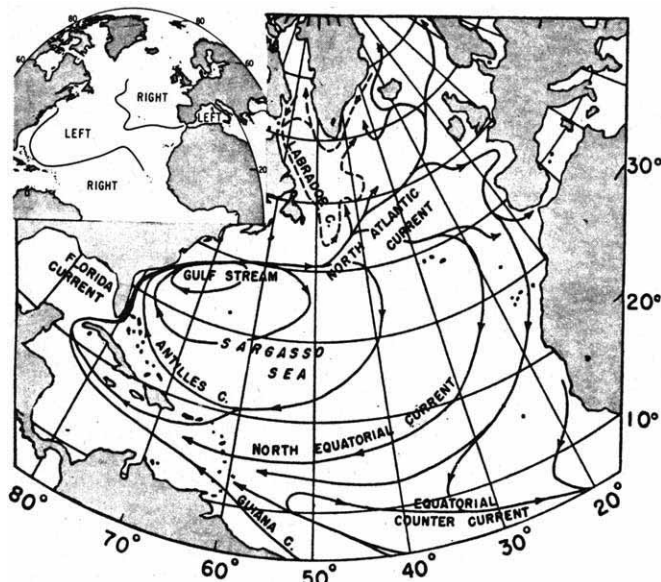


Fig. 1 Circulation of the North Atlantic according to Sverdrup *et al.*⁶. Inset, coiling of *G. truncatulinoides* in surface sediments from the North Atlantic after Ericson *et al.*⁴ and in the Mediterranean⁸⁻¹¹.

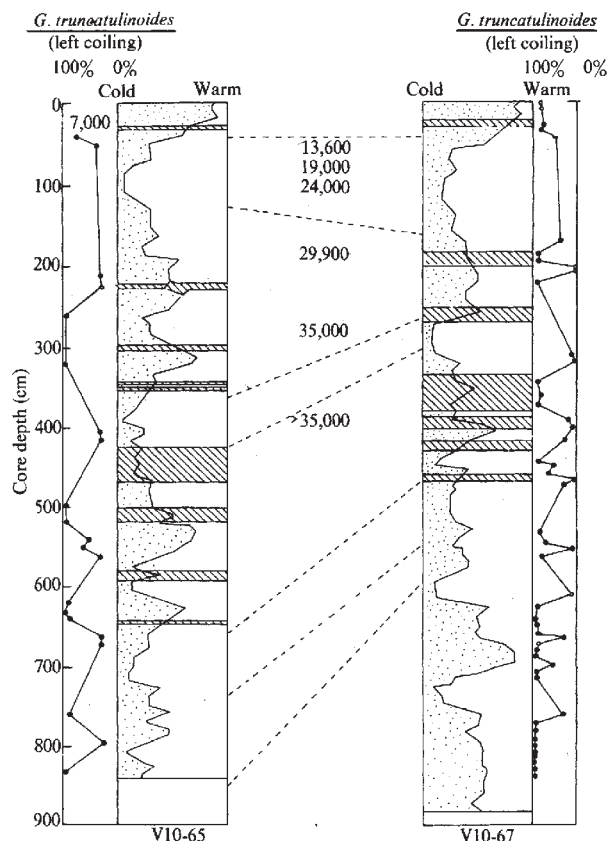


Fig. 2 Two sediment cores from the Mediterranean: V10-65, 34° 37' N, 23° 25' E, water depth 2,586 m; V10-67, 35° 42' N, 20° 43' E, water depth 2,890 m. Black sapropels (hatched areas) represent stagnant episodes. Climatic curves based on total planktonic faunal analysis (after ref. 9).

The time interval represented by the longest Mediterranean core exceeds 120,000 yr. Faunal evidence suggests that surficial water exchange between the ocean and the sea was virtually uninterrupted throughout this time. Consequently, when reconstructing the late Cainozoic climatic history of the Mediterranean, past oscillations in climates and circulation patterns of major current systems in the adjacent North Atlantic Ocean may be inferred with high degree of confidence.

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BIOLOGICAL SCIENCES

Morphine Physical Dependence unaltered by Previous Dependence on Morphine

AFTER a period of abstinence, narcotic addicts, if untreated with opioids, frequently relapse and resume self-administration of opioid compounds¹. Little is known about factors that influence relapse; it has been attributed to the addict's social environment and to his or her psychological need for the drug. An alternative possibility is that, because of previous exposure to opioids, post-addicts are biochemically more susceptible to the properties of opioids that produce physical dependence. Opioid compounds have long-term effects on the brain. Bound morphine persists in the rat brain for at least three weeks after a single dose². Tolerance to morphine was observed 1 year after a single dose of morphine to rats³ and evidence has been presented for an immunological theory of morphine tolerance⁴. In man⁵ and rats⁶ homeostatic disturbances resembling abstinence signs can be detected six months after the acute phase of withdrawal. By contrast with the reported chronic and persistent effects of morphine, Cheney and Goldstein⁷ have recently shown that the median effective dose of naloxone for precipitating withdrawal-jumping in morphine-dependent mice was unchanged by earlier dependence on morphine. As the evidence for long-term effects of morphine was obtained principally in rats, we have further studied morphine dependence in this animal to determine if previous exposure to morphine permanently alters the neural substrates for producing physical dependence on morphine.

Male Sprague-Dawley rats weighing 183–258 g (average 215 g) were used in all experiments. Morphine dependence was induced by subcutaneous implantation, under light ether anaesthesia, of a pellet containing 75 mg of morphine base^{8,9}. Controls were implanted with a pellet containing all the formulation ingredients of the morphine pellet except morphine. Seventy-two hours after morphine or placebo implants, the pellet was removed under light ether anaesthesia. We have

shown that, with this method, dependence on morphine in rats is maximal at 70–74 h after implantation (work in preparation). Morphine-implanted rats lost 8–10% of their initial body weight 1–3 days after removal of the pellet whereas placebo-implanted rats gained weight normally at 2% of body weight per day. A second pellet containing morphine was then implanted into all rats 5 days after removal of the first pellet; by this time rats previously implanted with morphine had the same growth rate as controls.

Physical dependence on morphine can be quantified by the frequency or intensity of abstinence signs observed after abrupt termination of opioid intake or after injection of opioid antagonists¹⁰. The degree of dependence was assessed here by precipitating the acute abstinence syndrome with intraperitoneal injection of the opioid antagonist, naloxone hydrochloride, 72 h after the second morphine implant.

Rats were placed in 1 gallon glass jars and abstinence precipitated after a 10 min adjustment period. Abstinence behaviour, continuously recorded for 10 min after naloxone injection, was quantified according to a ranking system based on the median effective dose (ED₅₀) of naloxone for precipitating different abstinence signs. In our experimental conditions, low doses of naloxone (0.02–0.1 mg/kg) elicited, in the morphine-dependent rat, ear blanching, abnormal posturing and diarrhoea. At intermediate doses of naloxone (0.1–0.5 mg/kg), abstinence signs that also appeared were teeth chattering, swallowing movements, some escape behaviour and wet shakes. At high doses of naloxone (0.5–10 mg/kg) wet shakes or repeated attempts to escape from the jar were precipitated in almost all animals. Abstinence intensity was therefore estimated according to the ranking system shown in Table 1; a unique abstinence rank being assigned to each rat. The validity of this ranking method is discussed elsewhere¹⁴.

Table 1 A Ranking System for Quantifying Precipitated Withdrawal

Abstinence behaviour	Abstinence rank
No change in behaviour	0
Abnormal posturing, ear blanching, diarrhoea (any two out of these three abstinence signs)	1
Teeth chattering or swallowing movements or salivation	2
Two or more escape attempts or three or more wet shakes	3

The animals were weighed before and 3 h after naloxone injection to calculate the loss of body weight during withdrawal. This parameter, in addition to behavioural signs, is a quantitative indicator of abstinence intensity¹¹. The Mann-Whitney U test¹² for differences in abstinence rank and Student's *t* test for differences in body weight were used.

As shown in Table 2, the intensity of the precipitated abstinence syndrome can be distinguished by the 2 doses of naloxone used for precipitating abstinence. The degree of abstinence for control animals precipitated with 10 mg/kg of naloxone is significantly greater than abstinence precipitated by 0.1 mg/kg of naloxone ($P < 0.02$). The magnitude of the body weight loss between the 2 placebo-implanted groups was

Table 2 Morphine Dependence in Rats Previously Dependent on Morphine

Pretreatments	Naloxone HCl dose (mg/kg)	% of animals in each abstinence rank				Mean abstinence rank	% Loss in body weight 3 h after naloxone HCl
		0	1	2	3		
Placebo implant (12)	0.1	8	17	42	33	1.9	5.7 ± 0.5
Morphine implant (11)	0.1	28	18	27	27	1.5	6.8 ± 1.1
Placebo implant (12)	10.0	0	0	8	92	2.9*	7.9 ± 0.7*
Morphine implant (12)	10.0	0	0	17	83	2.8	8.8 ± 0.8

* $P < 0.05$ vs placebo implanted rats injected with 0.1 mg/kg of naloxone HCl.

Pretreatment consisted of subcutaneous implantation of a pellet of 75 mg of morphine or of placebo, which was removed 72 h later. Five days after the end of pretreatment, each rat was implanted with a morphine pellet and 72 h later was challenged with an intraperitoneal injection of naloxone HCl. Numbers in parentheses refer to the number of rats in each group. Body weight data are tabulated as the mean ± s.e.

also significant ($P < 0.02$). Earlier dependence on morphine did not intensify the dependence produced by subsequent exposure to morphine as measured by the behavioural parameters and the body weight loss during precipitated withdrawal (Table 2).

Our results indicate that physical dependence on morphine is not increased by previous dependence on morphine. Factors contributing to the increased susceptibility of narcotic addicts to readdiction must therefore be due mainly to psychological dependence. Persistent physiological and biochemical changes induced by morphine may provide conditioned signals of the drug experience¹³ and accelerate relapse, but it appears that the neural substrate of opioid dependence is not permanently sensitized by previous dependence on morphine.

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Effect of Cyclic AMP on Morphine Analgesia Tolerance and Physical Dependence

ADENOSINE-3',5'-MONOPHOSPHATE (cAMP) has often been suggested as a second messenger which mediates the action of a variety of hormones¹. The presynaptic location of the cAMP system, and the demonstration of a cAMP dependent protein kinase in mammalian brain tissue, suggest a possible role for cAMP in the central nervous system². It has been suggested, for example, that cAMP may participate in the secretion of acetylcholine³ and the hypophyseal releasing factors in the hypothalamus³. *In vitro*⁴ and *in vivo*⁵ studies indicate that some putative neurohormones increase cAMP synthesis by activating adenyl cyclase. The effect of cAMP on brain biogenic amines has also been studied. Shein *et al.*⁶ showed an increase in serotonin (5-HT) synthesis from tryptophan by cAMP in pineal culture. Tagliamonte *et al.*⁷ reported that injection of cAMP into the lateral ventricle of rats increases the 5-HT turnover in brain. Results obtained in our laboratory in mice (I. K. H., H. H. L. and E. L. W., unpublished results) indicate that cAMP decreases the endogenous level of cerebral norepinephrine (NE) and dopamine (DA) as well as the conversion of ¹⁴C-tyrosine into ¹⁴C-CA (catecholamines).

The possibility that cAMP might interact with morphine is suggested by reports indicating that morphine can alter the functional state of the biogenic amines and that the latter substances can modify morphine actions⁸. It has been suggested^{9,10} that the role of brain serotonin (5-HT) may be involved in morphine actions even though others fail to agree (ref. 11, and unpublished results of H. H. L. *et al.*). Increased brain tyrosine uptake and catecholamine synthesis after morphine have also been noted (H. H. L. *et al.*, unpublished results). We now present evidence that cAMP antagonizes morphine analgesia and accelerates the development of morphine tolerance and physical dependence.

Male Swiss-Webster mice (Bio-Science, Oakland, and Simonsen Labs, Gilroy, California) weighing 20 to 25 g were rendered tolerant to and physically dependent on morphine as described previously by the subcutaneous implantation of a specially formulated morphine pellet¹¹. After 72 h the pellet was removed, and the degree of tolerance that had developed was obtained by determining the increase in amount of morphine required over that before pellet implantation to delay the tail-flick reaction time to thermal stimulus by three or more seconds ("analgesia"). Determination of the median analgesic dose of morphine (AD₅₀) was performed 6–7 h after removal of pellet at which time the tail-flick response time had returned to the mean pre-drug baseline between 1.2 and 1.7 s. The degree of dependence developing after 72 h of implantation was ascertained in other groups of mice by determining the median effective dose (ED₅₀) of the narcotic antagonist, naloxone, to precipitate withdrawal jumping¹¹. An inverse relationship exists between the two parameters. The challenge dose of naloxone was given subcutaneously 6–7 h after removal of the morphine pellet. cAMP was administered in saline solution immediately after pellet removal.

The administration of cAMP or one of its surrogates (dibutyl-cAMP, a phosphodiesterase-resistant cAMP analogue, and theophylline, a phosphodiesterase inhibitor) before morphine antagonized the analgesic effects of the latter compound in naive mice as evidenced by a more than doubling in the amount of morphine required to block the nociceptive response to thermal stimulus. The results are summarized in Table 1. Surprisingly, cAMP 10 mg/kg intravenously increased the morphine AD₅₀ as much as cAMP intracerebrally, but the maximum effect was not reached until 6 h later. Dibutyl-cAMP and theophylline also increased the morphine AD₅₀ to a comparable degree. Subjectively, the antagonism of morphine effects by all three compounds appeared to persist for at least 24 h.

Table 1 cAMP Antagonism of Morphine Analgesic Activity in Naive Mice

Treatment	Route of administration	Dose mg/kg	H after administration	Subcutaneous morphine AD ₅₀ *
Saline	Intracerebral†	—	1	4.0 (3.2–5.0)
	Intraperitoneal	—	6	3.8 (2.6–5.5)
cAMP	Intracerebral†	0.14	1	11.0 (6.7–18.2)
cAMP	Intravenous (once)	10	6	10.0 (8.3–12.0)
	Intravenous (3 times)‡	10	30	10.2 (8.7–12.0)
Dibutyl cAMP	Intravenous	10	6	9.5 (8.2–11.0)
Theophylline	Intraperitoneal	100	6	8.0 (5.3–12.0)

* Figures in parentheses denote 95% confidence limits.

† In a volume of 14 µl.

‡ cAMP was injected daily for 3 days.

The antagonistic effect of cAMP on morphine analgesia was also evident in tolerant mice. In animals rendered highly tolerant by pellet implantation, a single injection of cAMP increased the morphine AD₅₀ by two-fold (Table 2), which is similar to that noted in non-tolerant animals (Table 1). With repeated cAMP administration there was an even greater

antagonism of morphine analgesia, even though the AD₅₀ estimation was not performed until 30 h after the last cAMP administration; the morphine AD₅₀ in this group was increased more than four-fold (Table 2). That the augmented antagonism was not dependent on the animals receiving a greater number of cAMP injections is indicated by the fact that, in non-tolerant animals, three previous injections of cAMP yielded the same increase in morphine AD₅₀ as a single injection (Table 1). We interpret this to mean that cAMP affects not only the response to morphine in the tolerant animal but the development of tolerance as well.

Table 2 Effect of cAMP on Morphine Tolerance and Physical Dependence

Treatment	Intravenous injection schedule* h before pellet removal				Morphine AD ₅₀ † mg/kg (95% C.L.)	Naloxone ED ₅₀ ‡ (0.26–0.68)
	72	48	24	0		
Saline control	S	S	S	S	105 (73–150)	0.42 (0.26–0.68)
Acute cAMP†	S	S	S	A	230 (163–324)	0.40 (0.29–0.55)
Chronic cAMP§	A	A	A	S	450 (357–567)	0.07 (0.06–0.08)

* S = saline 0.15 ml.; A = cAMP, 10 mg/kg.

† Determinations were made 6–7 h after pellet removal.

‡ Administered after development of tolerance and dependence.

§ Administered before and during development of tolerance and dependence.

The repeated administration of cAMP, besides increasing the rate of development of tolerance to morphine antinociception, appeared to enhance considerably the precipitated withdrawal jumping response to naloxone in morphine-dependent mice. As shown in Table 2, a single administration of cAMP did not alter the naloxone ED₅₀ but, after repeated daily administration during the three day implantation period, enhanced jumping was indicated by the fact that the naloxone ED₅₀ was decreased to about one-sixth of its control values. Subjectively, other withdrawal signs (circling, rearing, weight loss, urination) were also more readily apparent after cAMP treatment.

The antagonism of morphine analgesia by cAMP appears to be associated with the biogenic amines. Our preliminary studies indicate that the administration of dihydroxyphenylserine (DOPS) to elevate brain norepinephrine largely antagonized the cAMP induced increase in the morphine AD₅₀ whereas increasing brain 5-HT with the precursor tryptophan enhanced the effects of cAMP. Increasing brain 5-HT and catecholamines by inhibiting their destruction with the monoamine oxidase inhibitor, pargyline, resulted in antagonism of the cAMP effects. It would appear therefore that elevating brain catecholamines is more critical than lowering 5-HT for reversing cAMP antagonism of morphine antinociception.

Part of this study was presented before the American Society of Pharmacological Experimental Therapy in Burlington, Vermont (August 1971) (see *Pharmacologist*, Vol. 13, Abstract Nos. 678 and 679).

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Effect of Copper on the Preimplantation Mouse Embryo

COPPER wire wound around a portion of an intrauterine contraceptive device (IUD) greatly increases the effectiveness of the device¹—the pregnancy rate, side effects, and expulsions are all decreased. These effects are related to the amount of wire present on the device in the uterus². Although the exact mechanism by which the copper wire acts is not known, the effect is local, and there is evidence that the copper changes the endometrium. Another possible site of action of the copper is on the developing embryo within the uterus. Chang and Tatum³ demonstrated that blastocysts, briefly exposed to copper wire *in utero*, were able to develop when placed in normal uteri. Another study⁴, however, indicated that the blastocysts in copper-containing uteri disappear before implantation.

We report here a series of experiments *in vitro* to clarify the direct effect of copper on the embryo; these demonstrated that copper is toxic to the embryo.

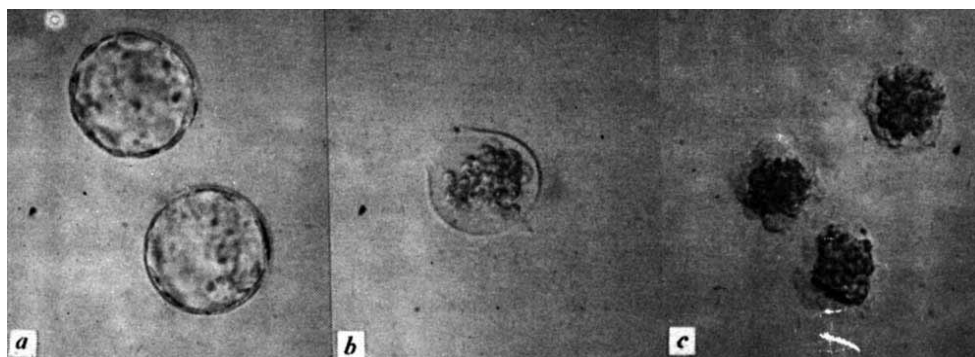
The techniques for obtaining, handling, and culturing the embryos have been previously described^{5,6}. Embryos were placed in small droplets (50 μ l.) of the test medium under 10 ml. of sterile silicone oil in a tissue culture dish and the effect of the medium on development determined. The basic medium used throughout these experiments was Brinster's Medium for Ovum Culture-2 (BMOC-2), which is a modified Krebs-Ringer bicarbonate solution containing 2.5×10^{-4} M pyruvate and 1 mg/ml. bovine serum albumin (BSA)^{6,7}.

First, two-cell embryos were placed in medium containing CuCl₂ in concentrations between 10^{-4} and 10^{-5} M, and the number of blastocysts which developed after three days in culture was determined. The results of these experiments indicate that copper has a dramatic effect on the development of the early mouse embryo. Concentrations of 2.5×10^{-5} M CuCl₂ and higher kill two-cell embryos, whereas embryos in lower concentrations develop into blastocysts. In addition to killing the embryos, the higher concentrations of copper appeared to dissolve the zona pellucida of a few embryos.

Because mouse embryos enter the uterus early on day 4 as morulae or early blastocysts and because the copper IUD is likely to affect mainly blastocyst stages within the uterus, in the next experiments the effect of CuCl₂ on the development of early blastocysts over a 24 h period was determined. Two levels of albumin were employed in the culture medium to determine the effects of possible protein-copper interactions on blastocyst survival. The results of these experiments are shown in Table 1 and demonstrate first that the mouse blastocyst is about as sensitive to the toxic effect of CuCl₂ as two-cell embryos and, second, that the effects of the copper on the blastocyst occur in less than 24 h. In addition, the experiments show that albumin protects the blastocyst from the copper, in direct proportion to the amount of albumin present.

Second, small lengths of copper wire (0.004 inch in diameter) were placed in the drops of culture medium. The effect of the copper wire was even more dramatic than the effect of CuCl₂. The results of these experiments are shown in Table 2. Very small pieces of wire killed the blastocyst and dissolved the zona pellucida (see Fig 1). Recent work has shown that

Fig. 1 *a*, Two blastocysts completely surrounded with normal zonae pellucidae; *b*, a dead blastocyst with zona pellucida partly dissolved; *c*, three dead blastocysts with zonae pellucidae completely dissolved.



Cu^{2+} is liberated from metallic copper strips at the rate of approximately $8.4 \times 10^{-10} \text{ mol h}^{-1} \text{ mm}^{-2}$ in a saline solution containing 1 mg/ml. of BSA and at approximately $14.2 \times 10^{-10} \text{ mol h}^{-1} \text{ mm}^{-2}$ in a saline solution containing 10 mg/ml. of BSA^{8,9}. Because the culture medium is similar in ionic content to saline, the amount of Cu^{2+} liberated in 24 h from a 0.1 mm length of wire is estimated to be approximately $6.6 \times 10^{-10} \text{ mol}$ in 1 mg/ml. BSA and $11.2 \times 10^{-10} \text{ mol}$ in 10 mg/ml. BSA. This would produce in 50 μl . a copper concentration of about 1.33×10^{-5} and $2.25 \times 10^{-5} \text{ M}$ respectively. In the medium containing 1 mg/ml. BSA, the effects of a 0.1 mm length of copper wire and $1.33 \times 10^{-5} \text{ M}$ CuCl_2 are similar (Tables 1 and 2). In the medium containing 10 mg/ml. BSA, however, the copper wire seems to be slightly more effective than might be expected on the basis of liberated Cu^{2+} . Oster^{8,9} has suggested that the metallic copper breaks S-S bonds in the protein thus changing the protein in the medium and contributing to the death of the embryo. The much greater dissolution

Table 3 Speed of Action of Copper Wire on Early Blastocysts

Length of copper and concentration of albumin	Incubation time (h)						
	0.5	1.0	2.0	4.0	5.0	6.0	24.0
1 mm wire 1 mg albumin/ml.	0*	0	0	10	10	10	10
2 mm wire 1 mg albumin/ml.	10	10	10	10	10	10	10
2 mm wire 10 mg albumin/ml.	0	2	7	10	10	10	10
2 mm wire 70 mg albumin/ml.	0	0	0	0	0	0	6

* The number of blastocysts dead from 10 early blastocysts placed in culture.

of the zona pellucida in drops containing copper wire than in drops with CuCl_2 might also be due to some direct action of metallic copper.

Third, the rapidity of action of copper wire on early embryos was determined (Table 3). It is clear that the speed of action increases as the surface area of copper wire increases and decreases as the protein concentration increases. The short time in which the wire kills the blastocysts in some experiments is striking, particularly since the surface area of the wire is much less than employed on the IUD. A wire 1 mm in length has a surface area of 0.33 mm^2 , whereas the surface area of the wire used on the human intrauterine device is generally between 30 and 200 mm^2 .

Our studies suggest that if the human blastocyst is as sensitive to copper wire as the mouse blastocyst, the copper IUD could adversely affect the development of the blastocyst even in the fluid volume of the uterus.

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Table 1 The Effect of Copper Chloride on the Development of Early Blastocysts into Late Blastocysts

Concentration of CuCl_2 (M)	Albumin concentration 1 mg/ml.		Concentration of CuCl_2 (M)	Albumin concentration 10 mg/ml.	
	Rep 1	Rep 2		Rep 1	Rep 2
1.0×10^{-4}	0	0	1.0×10^{-3}	0	0
7.5×10^{-5}	0	0	7.5×10^{-4}	0	0
5.0×10^{-5}	0	1	5.0×10^{-4}	0	0
2.5×10^{-5}	7	6	2.5×10^{-4}	10	9
1.0×10^{-5}	10	9	1.0×10^{-4}	10	10
0	10	10	0	10	10

The values are the number of late blastocysts which had developed from 10 early blastocysts and were alive after 24 h in culture.

Table 2 The Effect of Copper Wire on the Development of Early Blastocysts into Late Blastocysts

Length of copper wire in mm	Albumin concentration 1 mg/ml. Blastocysts		Albumin concentration 10 mg/ml. Blastocysts	
	Dead *	No zona †	Dead *	No zona †
1.00	30	20	18	9
0.75	30	8	16	9
0.50	30	12	6	1
0.25	30	7	2	2
0.12	21	2	7	1
0.06	3	3	0	0
0.00	1	0	0	0

There were three separate experiments at each albumin concentration with 10 early blastocysts in each drop at the beginning of culture.

* Number of blastocysts dead after 24 h in 50 μl . of culture medium containing copper wire.

† Number of dead blastocysts from which the zona pellucida had completely disappeared. The zona was not dissolved on blastocysts that lived.

Origin of Amniotic Fluid Group-specific Component

THE use of amniotic fluid for the prenatal diagnosis of genetic disease has prompted investigations into the origin of amniotic fluid protein. Several observations (refs. 1-5 and R. G. S. and D. J. H. B., manuscript in preparation) have suggested that the foetus contributes protein to the fluid early in pregnancy, and it has also been claimed that during this time amniotic fluid is an extension of the foetal extracellular space^{6,7}. Conversely, in term amniotic fluid, the serum proteins transferrin and group-specific component (Gc) have been found to be of maternal origin⁸⁻¹⁰. Serum proteins make up the great majority of amniotic fluid protein at all stages of gestation, but it is not known whether maternal or foetal serum is the source early in gestation. In this study, Gc polymorphism is used to investigate this point.

Polymorphism studies on Gc protein have shown that the protein in foetal serum is synthesized by the foetus from ten weeks of gestation onwards¹¹. Thus, in cases where the foetal phenotype is discordant with the mother's, the amniotic fluid Gc would be concordant with the maternal phenotype if it is of maternal origin, but discordant if it is of foetal origin. In the latter case, the expected frequency of discordance between the foetal and maternal phenotypes is equal to the heterozygote frequency in the population¹².

Antibody-antigen crossed electrophoresis (AACE) is known to show Gc as a heterogeneous protein¹³, but has not been previously used for Gc phenotyping. We used the method as it allows a detailed examination of the amniotic fluid Gc pattern without previous concentration of the fluid, and is sensitive enough to show small contributions from one or other allele. AACE was carried out using 1% agarose and the buffer systems of Hirschfeld¹⁴. The first dimension was run at 6 V cm⁻¹ for 3 h, and the second dimension at 1.5 V cm⁻¹ for more than 15 h. The antiserum was raised in rabbits by subcutaneous injection of $\times 10$ concentrated amniotic fluid, which was dispersed in Freund's complete adjuvant for the first three injections. Amniotic fluid samples before 20 weeks of gestation were obtained at terminations of pregnancy, and thereafter at amniocentesis in cases of suspected rhesus isoimmunization. The Gc precipitate was identified in the gels by its characteristic heterogeneity^{13,14}, and also by the use of a specific anti-Gc antiserum (Behringwerke).

Table 1 Concordance and Discordance for Maternal Gc Phenotype

Gestation (weeks)	Concordant pairs			Discordant pairs All phenotypes
	Maternal Gc phenotype 1-1	2-1	2-2	
10-18	11	8	2	0
19-27	5	5	2	0
28-38	14	8	1	0

Number of pairs studied in which concordance or discordance for Gc phenotype was found between the amniotic fluid and maternal serum, broken down according to gestational age and maternal Gc phenotype. Phenotype frequencies: 0.54; 0.38; 0.09.

Table 1 shows that concordance of phenotype was found in all of the fifty-six maternal serum-amniotic fluid pairs studied. From the frequency of heterozygotes, approximately 38% discordance in at least one of the gestational groups would be expected if there were a major foetal contribution to the Gc of amniotic fluid. Among the cases summarized in Table 1 were eleven in which a sample of foetal serum was available for phenotyping. In four of these cases, discordance was found between the foetal and maternal phenotypes and, in each case, the phenotype of the amniotic fluid Gc was that of the mother.

From these results we conclude that throughout gestation the Gc in amniotic fluid is of maternal origin, and that it

enters the fluid by passing through the placental or reflected membranes. This finding sounds a cautionary note for any attempts to carry out prenatal diagnoses of genetic disease either by direct screening of serum proteins or by linkage analysis using serum protein polymorphisms.

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New Antifertility Agent—an Orally Active Prostaglandin—ICI 74,205

A MONTHLY application of contraception has the advantage that it involves application of medication only in the event of suspected pregnancy such as delayed menses¹, thereby reducing the unnecessary exposure of healthy persons to drugs. An intravaginal application of prostaglandins (PGs) has been successfully used for this purpose in 11 women¹. Naturally occurring PGs need to be administered in high doses to obtain termination of pregnancy by the oral route, however, and the effective doses have side effects such as vomiting, nausea and diarrhoea¹. It would be desirable to develop an analogue of natural PG active orally in doses which have no undesirable side effects, and with this rationale in mind we developed a C-22 derivative (Fig. 1) of PGF_{2α}—ICI 74,205 which appears to be some 20 times more potent orally than the parent PG in terminating early pregnancy in hamsters.

The antifertility properties were tested in pregnant hamsters as this species is known to be more sensitive to PGF_{2α} than rats². Adult hamsters were caged with fertile males at an appropriate stage of the oestrous cycle, and the day when spermatozoa were found in the vaginal smear was considered day 1 of pregnancy. Unless stated otherwise, all PGs were racemic. They were dissolved in phosphate buffer (pH 7.4) and administered either subcutaneously or orally once a day as indicated in Table 1. Animals were usually killed 48 h after

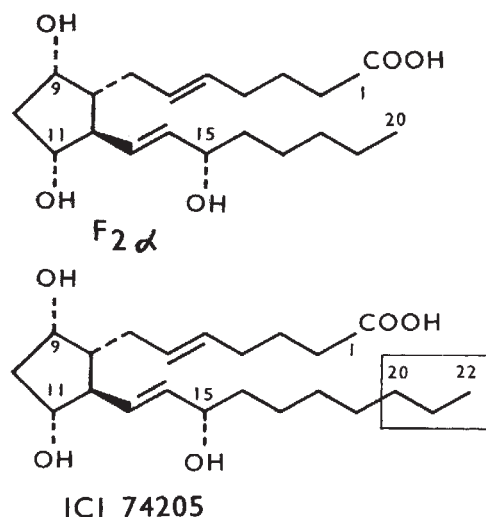


Fig. 1 Structural formulae of prostaglandin F₂α and ICI 74,205. The area in the square highlights the structural difference from F₂α.

20 times more potent than racemic PGF₂α in terminating early pregnancy in hamsters.

A single subcutaneous injection of PGF₂α on day 4 (autopsy on day 8) resulted in a loss of pregnancy (Group L), but the same effect could be achieved with 0.10 mg/kg (or 10 µg/hamster) of ICI 74,205 injected on day 4 or 5 (Groups M and N), again demonstrating the superiority of ICI 74,205 as an antifertility agent.

No significant side effects, such as diarrhoea or loss in body weight, were observed in the treated hamsters. Histological examination of ovaries from hamsters treated with ICI 74,205 showed degeneration of the original set of corpora lutea and a presence of a new set, suggesting fresh ovulations during the course of the treatment. This was confirmed by finding tubal ova in a high proportion of treated hamsters. Many treated hamsters showed atypical vaginal discharge during the course of the treatment, suggesting a premature termination of luteal function.

Additional experiments have shown that ICI 74,205 has no inherent oestrogenic, anti-oestrogenic, androgenic or anabolic activity. Its antifertility effects can be prevented by simultaneous administration of exogenous progesterone. When tested *in vitro* on uterine strips from guinea-pigs in dioestrus

Table 1 Antifertility Effects of PGF₂α and ICI 74,205 in Hamsters

Compound	Group	Dose (mg/kg)	Method of dosing	Duration (days)	Day of autopsy	No. pregnant No. treated	Body wt. change %
Buffer control	A	0.2 ml.	S.c.	4-6	8	10/10 (0)§	+5.3
PGF ₂ α	B	0.5	S.c.	4-6	8	0/11 (100)	-2.4
	C	0.25	S.c.	4-6	8	5*/11 (54)	-0.6
ICI 74,205	D	0.10	S.c.	4-6	8	0/12 (100)	+3.4
	E	0.05	S.c.	4-6	8	3*/7 (62)	-1.4
PGF ₂ α	F	20.0	Oral	4-6	8	0/3 (100)	-8.4
	G	10.0†	Oral	4-6	8	0/5 (100)	0
	H	10.0	Oral	4-6	8	2/3 (33)	+4.7
	I	7.5†	Oral	4-6	8	4/4 (0)	0
ICI 74,205	J	1.0	Oral	4-6	8	0/8 (100)	-6.8
	K	0.75	Oral	4-6	8	3/5 (40)	+24.8‡
PGF ₂ α	L	0.5	S.c.	4	8	2/7 (67)	+5.2
ICI 74,205	M	0.1	S.c.	4	8	0/4 (100)	+2.9
	N	0.1	S.c.	5	8	0/3 (100)	+1.0

* Embryos resorbing. † Isomerically pure (L) F₂α; all others racemic.

‡ Killed on day 15. § Numbers in parentheses denote %

termination of pregnancy.

the last injection, and the number of implantation sites counted. The pregnancy was considered to have been terminated when placental scars alone were visible in the uterus. Animals with even a single normal foetus, regardless of whether or not they had other resorbing foetuses, were considered pregnant.

Administration of PGF₂α at a daily dose of 0.5 mg/kg subcutaneously from days 4 to 6 inclusive terminated pregnancy in 100% of hamsters (Group B, Table 1) while all control hamsters injected with phosphate buffer were pregnant (Group A). The dose of ICI 74,205 required to obtain 100% termination of pregnancy, by contrast, was 0.1 mg/kg/day (Group D), suggesting that the compound was five times more potent than PGF₂α.

When administered orally from days 4 to 6, a daily dose of 20 mg/kg PGF₂α was required to obtain 100% termination of pregnancy (Group F) while the lower dose (10 mg/kg) was inactive (Group H). A limited availability of racemic PGF₂α led us to use isomerically pure PGF₂α (1 isomer) for further evaluation of oral activity (Group G). A daily dose of 10 mg/kg was required; a lower dose (7.5 mg/kg) proved inactive (Group I). By contrast, ICI 74,205 caused a complete termination of pregnancy when given orally from days 4 to 6 at a daily dose of only 1 mg/kg (Group J), indicating that ICI 74,205 was

(that is, days 4-6 of the cycle), the compound showed less than 35% of the smooth muscle stimulating activity of PGF₂α (racemic) and less than 1% of PGE₁ (L isomer).

Our results show that a lengthening of the lower side chain results in a preferential enhancement of oral activity of the compound. The data illustrate the fact that it is possible to modify the prostaglandin molecule chemically, and to alter its biological properties in a potentially useful manner.

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Culture of Rabbit Blastocyst in a Medium with a Convection Current

ALTHOUGH mammalian embryos have been cultured successfully in a recirculating medium continuously recharged with gas¹⁻⁴, our attempts at rabbit blastocyst culture in such a system were not always as satisfactory as anticipated⁴. The blastocystic membrane usually ruptured, followed by collapse of the whole embryo within two to three days. One explanation was that the embryonic disk was pressed against the wall of the culture chamber because of its own buoyance, and therefore designed a new system in which recirculation was achieved by a convection current induced by point heating from a cautery (Fig. 1).

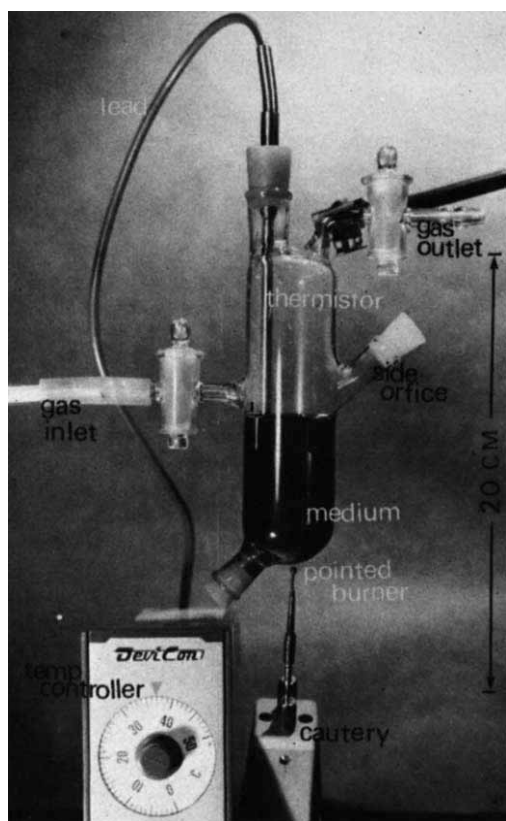


Fig. 1 Culture system for rabbit embryos in a medium with convection current. The centre chamber has a diameter of 4 cm and is 14 cm high. The thermistor has a stainless steel shield.

Nutrient solution (50 ml. of medium 199⁵ (Nissan), supplemented with 20% calf serum, 10% 'Difco' bacto-tryptose phosphate and 50 mg/l. of sodium pyruvate) and two embryos were introduced into the central chamber from a side opening. The solution temperature at the tip of the thermistor was regulated at $37 \pm 0.2^\circ \text{C}$. The gas mixture of 5% CO_2 in air with a flow rate of 130 ml./min was humidified by bubbling through a water trap and introduced into the cell through a filter tube packed with sterilized cotton. After 10 min, the outlet and inlet tubes were closed. When the outside temperature was 20° or 27°C , the working time of the cautery point was 1.8 or 1.2 min, with intervals of 1.1 and 2.1 min respectively.

Usually, one-third of the medium was renewed after 48 h, and the gas in the chamber was renewed every 24 h. Embryos were removed after 3 or 4 days and examined with an inverted microscope.

We have studied about 100 rabbit blastocysts explanted 6 days 15–18 h post coitum (Fig. 2a), of which seventy-eight and seventeen were cultured for 2 and 4 days respectively.

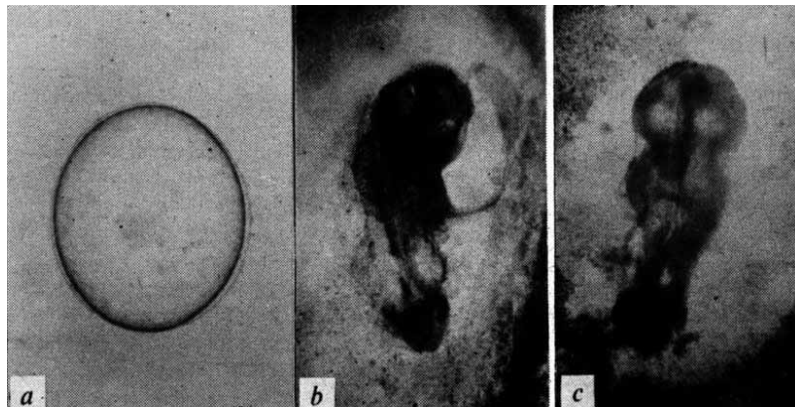
Gross examination with a magnifying glass from outside the chamber showed that eighty-six of the embryos were viable and undamaged in this system after 12 h of culture. In 3 days, they grew from the preprimitive streak stage to the first somitic stage. When development passed beyond the 18–20 somite stage, disintegration of the somite mass into mesenchyme often made it impossible to count the somites, although about 90% (sixty-two out of sixty-nine) viable and undamaged embryos reached the neural fold stage after 3 days of culture. In 70% (forty-three out of sixty-two) embryos, the neural tube closed, and there were optic vesicles, beating heart and amnions in various stages of closure (Fig. 2b and c). In some of these specimens a small vesicular organ, similar to a limb bud, and a blood-filled vesicular network developed.

In all living specimens the formation of a germinal disk followed by further systematic development took place at the upper region of the floating blastocysts. There was, however, a tendency for the region of the embryonic disk to rotate gradually about the central axis after 2 days, and there were signs of stunting in the posterior regions, with an outgrowth of trophoblast. Fourteen embryos removed after 4 days of culture, and previously described as viable, showed acute lateral bending of the axis, with the appearance of fluid-filled vesicles in many tissues and coronary arrest in all cases.

These results suggest that a shift of the centre of gravity would be responsible for the rotation by increased mass of the embryonic area and, moreover, that the rotation might lead to malformation of embryo by arresting development.

This new system may provide a culture environment that supports the development of rabbit embryos from the pre-primitive streak stage to beyond the eighteen-somite stage in a high proportion of cases. It is simple and convenient for laboratory use. We suggest that this apparatus could also be used for the culture of a more early stage of mammalian eggs *in vitro*.

Fig. 2 Rabbit embryos at the start of the culture and after 3 days culture in a medium stirred by convection current. a, Blastocyst explanted for cultivation, at the stage of the preprimitive streak and embryonic shield ($\times 10$). b, Embryo of more than 18 somites with a sign of malformation (cervical flexure) ($\times 20$). c, Embryo of more than 20 somites ($\times 20$).



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Sexual Selection for Colour Phases in the Arctic Skua

ACCORDING to Darwin¹, males who mate early in the breeding season gain a selective advantage. If the males of a species of bird, for example, establish their territories before the females come to breed, then the first females to arrive will mate either with males who have successfully maintained their territories or with those whom the females prefer. Darwin assumed that females who had had better nourishment before the beginning of the breeding season would breed earlier and rear more offspring, and, therefore, the males who mated first would also gain an advantage. Only some of the females may have particular mating preferences. A computer model, allowing for partial female mating preferences, showed that the preferred males can gain an advantage even when the earlier breeding pairs are not the fitter². The selection is frequency-dependent and can produce stable polymorphisms when balanced by natural selection.

In computer simulations of sexual selection², I used the fitness function of breeding time in the Arctic skua, a sea bird which breeds on islands in the North Atlantic. The function $w = 1 - (\theta - x)^2 / \phi$ gave a good fit for the breeding data of the Arctic skua on Fair Isle. x is the breeding time in weeks from the date of hatching of the first egg. θ is the optimum breeding time when the relative fitness is at a maximum, w is the fitness, and ϕ is a constant. Values of $\theta = 0.47354$ and $\phi = 24.254$ were calculated from my data³.

The Arctic skua is of genetic interest because it is polymorphic for three colour phases, dark, intermediate and pale. (Pale has white feathers on its underparts, intermediate has brown feathers with white bases and dark has completely brown feathers.) O'Donald and Davis⁴ studied the genetics of the polymorphism and concluded that two alleles determined the three phases. Berry and Davis⁵ have analysed the data from Fair Isle according to sex as well as phase. They found there is an excess of pairs in which the male is darker than the female. Also, dark males mate before dark females, and sexual selection may thus favour the darker males. Berry and Davis divided their data into new and older pairs. The new pairs are not necessarily those breeding for the first time (as in my own classification⁶), but include all those who have bred before but changed mates, forming about 20% of all pairs. Pairs breeding for the first time are much less successful in fledging their young than more experienced pairs but they also breed much later and are no less successful than experienced pairs breeding equally late. I shall assume that all pairs have the same fitness function in relation to breeding time.

Sexual selection can affect only new pairs. Berry and Davis take June 19 as the origin, using the hatching of the first egg

as the breeding date. Among new pairs, dark males bred at a mean date of 7.4, intermediate males at a mean of 12.0 and pale males at a mean of 18.3. All three phases of female bred at around the mean of 11.8 with no significant difference in breeding date. The differences between the males are highly significant, and can be explained if the females exercise a mating preference in favour of darker males but are not themselves selected. In terms of my distribution of breeding time in weeks³, the day June 19 occurs at point $x = 6/7$. Therefore, in weeks, the mean for dark males, $\bar{x}_D = 13.4/7$; for intermediate males, $\bar{x}_I = 18/7$; for pale males, $\bar{x}_P = 24.3/7$. The mean fitness is given by $\bar{w} = 1 - (\theta - \bar{x})^2 / \phi - V_x / \phi$. Using the variances within each phase for the value V_x , we obtain the mean fitnesses of the phases as follows.

$$\bar{w}_D = 0.883$$

$$\bar{w}_I = 0.765$$

$$\bar{w}_P = 0.580$$

Therefore the sexual selective coefficients measuring the relative disadvantage of intermediate and pale males are

$$s_I = 0.13$$

$$s_P = 0.34$$

These selective coefficients are high because intermediate and pale males breed very late in the breeding season when fledging success is low. The darks are at a considerable advantage. In my computer simulations of sexual selection using the distribution of the Arctic skua's breeding times, I found that selective coefficients as high as this could only occur if the mating preference were complete. But this need not be so for the selection among new pairs. Their distribution of breeding times is very different from the overall distribution: their mean breeding time is 2.514 weeks while for all pairs the mean is 1.591. The new pairs are breeding at a time when the fitness is rapidly decreasing. The optimum is in fact 2.4 standard deviations ahead of their mean breeding time and their variations in fitness will therefore be much greater than those of the whole population.

When new pairs are omitted from Berry and Davis's data, there is still a residual effect of earlier breeding among the darker males, though the differences in breeding time are much less and give selective coefficients of only about 0.02 to 0.03. Among the females, however, the opposite effect is shown; the paler females breed earlier with a similar advantage about 0.02. The selective coefficients of the males in new pairs, however, are very high and should produce an increase in dark phases; yet on Fair Isle the frequencies of the phases appear to be stable⁴. This may be a stable polymorphism balanced either by natural selection or by migration of pales from the north where they are common.

The data on breeding time and colour phase of the Arctic skua suggest that sexual selection may be an important factor in the maintenance of its polymorphism. Sexual selection is only just beginning to be studied in the same intensive way that natural selection has been studied, yet sexual selection has the same inductive basis as natural selection. Darwin argued inductively from the adaptive significance of differences between races to the adaptive significance of differences within races: variations within a race may differ in fitness just as variations between races apparently do. In the same way, most sub-species and species of animals are reproductively isolated. Dobzhansky and Pavlovsky⁷ produced "ethological isolation" by the evolution of mating preferences in a laboratory experiment. Sexual isolation can thus depend on different mating preferences in different species. Hence we may argue, as Darwin argued in favour of natural selection, that differences within species will also be selected as a result of mating preferences. Sexual selection may be as important as natural selection in determining the evolution of many characteristics

and in maintaining balanced polymorphisms. In monogamous animals, variations in fitness at breeding time should provide a general mechanism by which a mating preference can produce a selective advantage.

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Ecological or Phylogenetic Interpretations of Crocodilian Nesting Habits

NESTING habits within the Crocodilia range from simple excavation of a hole for egg deposition (as in most reptiles) to the construction of mounds of vegetation or other materials in which the eggs are deposited. Nests constructed by some Crocodilia show a considerable advance over those of any other reptilian group; this ability of the Crocodilia has been widely discussed. Wermuth¹ interpreted the available data to indicate that all possible gradations from simple hole nesting to elaborate mound construction were represented. Greer², following Schmidt³, believes that nesting habits may indicate relationships, and has recently divided the group into hole versus mound nesting categories and discussed the evolutionary significance of this dichotomy.

Neill⁴ has argued that the nesting habits of crocodilians are ecologically related, with mound nesting habits associated with marshy environments and the hole nesting habit with nesting on banks. This view has subsequently been adopted by Greer⁴ juxtaposed with his original phylogenetic argument. Although the value of such an ecologically responsive character as a phylogenetic indicator may be seriously questioned on logical grounds, additional complexities in the reproductive behaviour of crocodilians are now known which demonstrate that nest type is not necessarily a genetically fixed character in all species.



Fig. 1 Nest of *Crocodylus acutus* in Gatun lake, Canal Zone, Panama. Nest hole is approximately in the centre of the clearing.

Several species are now known to, or are suspected to, display both behaviours, both between populations and even within populations.

Crocodylus acutus, considered by Greer² and all other workers to be a hole-nesting crocodile^{3,5-7}, may display both hole and mound building behaviours in different portions of its range, and even within single populations. In some localities, Jamaica and some Central American areas, for example (Fig. 1), it deposits its eggs in a hole, but in other areas, such as some portions of Mexico⁴ and southern Florida, it builds well defined mounds (Fig. 2).



Fig. 2 Mound nest of *Crocodylus acutus* at Florida Bay, Florida.

In one locality, Florida Bay in the Everglades National Park, Florida, all nest types are utilized by the species (Ogden, personal communication). Some females construct mounds of large size (Fig. 2), some construct low, poorly differentiated mounds, and some are known to lay their eggs in holes. Ogden, who is studying this population, reports that one female constructed a low mound and then laid her eggs in a hole dug in the trail leading to the mound. It will be interesting to learn of any differential hatching success or survival between the two nest types in this area.

There are several other species which display both nesting habits. *Crocodylus moreletii*, in Mexico, is a mound-nesting species (ref. 4 and personal observations of Powell and of Campbell) where it nests in swamp or marsh, but there is evidence that it uses nests in holes where it occurs along shallow forested streams with extensive sand banks. *Crocodylus rhombifer* of Cuba is a hole-nesting species^{2,10}, but there is evidence to suggest that this is only partly true (Fernandez). The term used to describe the nest of this species by the original source, "nido", can be translated either "hole" or "nest" and an error in translation is possible. Other species for which both nest types are indicated are noted in Table 1.

Table 1 shows a surprisingly good relationship between hole nesting and habitation in large rivers and lakes, and mound nesting and habitation in swamps, marshes, and other low-lying situations. It is not evident which specific environmental condition is most important in determining the nest type: position of the water table, availability of suitable substrate for digging holes, or probability of drastic unpredictable fluctuations in water level, and so on.

In the light of the crocodile's unusual, for a reptile, learning capacity⁸ we may speculate that individual differences may be based on the ecological experience of specific females, but it may be more reasonable to expect that the particular nest type used, on the average, in a given area represents the most adaptive response to the particular set of environmental variables encountered in that area. But the phylogenetic scheme presented by Greer^{2,14} is based on characters which are both ecologically responsive and intraspecifically variable and may

Table 1 Nest Type and Species Ecology

Species	Nest type	Habitat
<i>Gavialis gangeticus</i>	Hole	Large rivers
<i>Crocodylus acutus</i>	Hole or mound	Coastal marsh, larger rivers and lakes
<i>Crocodylus intermedius</i>	Hole	Large rivers and lakes
<i>Crocodylus johnsoni</i>	Hole or mound ^{11,13}	Savanna creeks and rivers, pools
<i>Crocodylus niloticus</i>	Hole	Large rivers and lakes
<i>Crocodylus palustris</i>	Hole or mound ¹⁵	Diverse; marsh and swamp, lakes and rivers
<i>Crocodylus rhombifer</i>	Hole or mound*	Freshwater swamp and marsh
<i>Crocodylus siamensis</i>	Hole or mound ¹²	Rivers and river swamps, lakes
<i>Crocodylus cataphractus</i>	Mound	Rainforest, savanna, wooded or grassy
<i>Crocodylus novaeguineae</i>	Mound	Freshwater swamps and marsh
<i>Crocodylus porosus</i>	Mound	Salt marsh, large rivers, lakes
<i>Crocodylus moreleti</i>	Mound ⁴ †	Savanna, river swamp, marsh-bordered lakes
<i>Osteolaemus tetraspis</i>	Mound	Rainforest streams, ponds
<i>Alligator mississippiensis</i>	Mound	Diverse; ponds, rivers, swamps, etc.
<i>Alligator sinensis</i>	Mound ⁹	River flood plains, freshwater marsh and swamps
<i>Caiman crocodilus</i>	Mound	Diverse; marshes, swamps, ponds, lakes
<i>Melanosuchus niger</i>	Mound	Savannas, freshwater, marsh, grassy lakes
<i>Paleosuchus palpebrosus</i>	Mound	Swamp, forested pools and floodplains
<i>Tomistoma schlegeli</i>	Mound	Rivers and river swamps

* Fernandez (personal communication) reports that the nests of *C. rhombifer* are sand or soil mounds, or holes.

† Confirmed by Campbell and Powell.

Only species for which both data are available are included. References as in Greer² except as noted.

therefore be more properly interpreted as indicating ecological similarities rather than phylogenetic relationships.

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New Technique for the Study of Sperm Whale Migration

IN the southern hemisphere, female and young male sperm whales (up to about 39 feet long) are not normally found in higher latitudes than 40° S while large males occur in Antarctic waters¹⁻³; clearly many large bulls must migrate from the breeding areas into colder regions. Evidence of the return of large bulls to lower latitudes rests upon marking them in the Antarctic⁴ or external infestation by Antarctic *Cocconeis* or *Cyamus*⁵. Only a single mark⁵ has been recovered which provides direct evidence for the return north from Antarctic waters. This mark (USSR No. 650203) was fired on December 25, 1967, at 62° 22' S 26° 25' E and the whale was killed on May 13, 1968, off Durban. The small size of the male concerned (35 feet at death) makes this record rather surprising although Jørgensen⁶ did mention that the smallest whales from Antarctic waters were about 35 feet. Marking can provide information on only a small part of the whale population at considerable cost, freshness of the whale restricts the value of infestation as an indicator but the study of food remnants in sperm whale stomachs provides another method without these disadvantages.

I have been studying the stomach contents of sperm whales for several years^{7,8}, including collections made in the Antarctic, at Durban and Donkergat, South Africa, and in Western Australia. The main food of sperm whales in these areas is cephalopod. Although cephalopod flesh is quickly digested by the whale, the chitinous jaws or beaks are retained in the second stomach and are, apparently, vomited periodically, as they are seldom found in the gut below that point. From studies on the flesh remains⁸, it has proved possible to distinguish between cold water Antarctic cephalopods and those from temperate waters off Africa and Australia. Lower beaks from identified specimens have provided criteria for the identification of ingested lower beaks⁷⁻⁹.

Stomach contents of some of the whales at Durban include beaks of Antarctic squid (Table 1). The majority of these are *Moroteuthis ingens*, *Mesonychoteuthis hamiltoni*, *Gonatus antarcticus* and an undescribed species of *Moroteuthis*.

Of twenty-two female whales about 64% contained no Antarctic cephalopod beaks in their complete stomach contents. Antarctic species contributed 1.3% or less of all beaks in each of the remaining stomachs. The northern limit of the Antarctic cephalopods is not known accurately, but their limited presence in female whales suggests that it must be close to 40° S. Near this latitude the subtropical convergence¹⁰ probably acts as a faunal boundary¹¹.

Of twenty-nine male sperm whales examined at Durban, 17% had no Antarctic cephalopod beaks. In 50% of those with Antarctic beaks they contributed 1.7% or less of all lower beaks. Males 35 feet or less in length had few or no Antarctic beaks (Fig. 1), although in 60% of those over 37 feet Antarctic species contributed more than 9% of all lower beaks in each whale. This supports the observations that males less than 35 feet long do not normally go into Antarctic waters, and suggests that one male of only 37 feet did go far south. This male contained a greater percentage of an unidentified species of cephalopod than any other whale, and its previous movements may therefore have been rather unusual.

The percentage of Antarctic beaks in those males with more

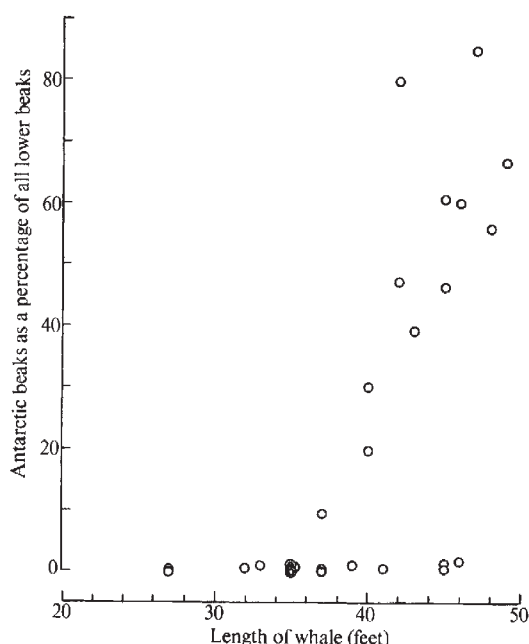


Fig. 1 Percentage of lower beaks belonging to Antarctic species in stomach contents of male sperm whales caught off Durban.

than 9% seems to increase with the size of the whale. If temperate and cold water species had a very broad overlap, this increase with size could result from larger whales migrating further south than smaller whales. Another possible explanation is that smaller whales take longer to travel to Durban from the Antarctic and therefore eat more on the

way. Those whales with over 80% of Antarctic beaks must have eaten very little during the swim from the Antarctic. The distance from 40° S to the Durban area is 600 nautical miles and, as sperm whales cruise at 3–5 knots¹², they probably take less than 8 days; even so, such a long swim with little food is remarkable in such an active mammal.

Clearly the beak method has considerable potential for studying migration to and from Antarctic waters, but its extension to other areas and its use in the study of smaller scale movements rest upon a more detailed knowledge of cephalopod distribution. Study of the cephalopods in stomach contents from a broad geographical area may yield such detail. For example, analysis⁸ of 117,519 lower beaks from 152 sperm whales caught off Donkergat and off Durban shows that one species of *Histioteuthis* (probably *H. meleagroteuthis*) contributes 14.34% of all lower beaks and some flesh at Donkergat but beaks are rare and flesh is absent at Durban. This is good evidence that sperm whales do not normally migrate from west to east round South Africa, and suggests that the breeding stocks of these two regions may be isolated. This agrees with Best's⁵ conclusion based on mark returns and breeding seasons¹⁵.

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Table 1 Lower Beak Collections from Whales caught off Durban

Sex	Whale length (feet)	Month	No. lower beaks	Antarctic species %
Females	32	5	1,043	0.1
	34	2	7,855	0.2
	34	3	3,523	0.2
	34	3	2,410	0.3
	35	2	1,012	0.1
	35	3	4,447	1.3
	35	3	347	0.6
	37	3	1,610	0.1
Males	27	2	368	0.3
	32	2	2,545	0.3
	33	3	204	1.0
	35	4	1,031	0.1
	35	6	3,762	0.3
	35	7	876	0.6
	37	7	947	0.1
	37	9	313 *	9.5
	39	6	1,105	1.0
	40	7	263	30.1
	40	7	1,692 *	19.8
	41	2	237	0.4
	42	7	388	47.1
	42	8	120	80.0
	43	8	168	39.3
	45	9	161	46.5
	45	6	869	1.3
	45	5	189 *	60.8
	45	9	426 *	0.4
	46	6	1,634 *	60.1
	46	10	783 *	1.7
	47	6	40 *	85.0
	48	5	1,911	56.1
	49	5	21 *	66.7

* Samples from stomachs. The remainder were from collections of the complete stomach contents. Whales with no Antarctic species are not included.

Motion Stereoscopy

ON June 1 I saw the most exciting visual spectacle that I have ever known. With two or three others, I was watching water running down the spillway of the big new dam at Cow Green in Upper Teesdale. The main flow consisted of a continuous sheet, causing enough foam to make it easily seen, but it was a windy day and little waves in the reservoir were splashing over to give a series of extra water masses which formed themselves into broad pointed jets running down the spillway faster than did the main mass.

As I watched, the flat sheet quite gradually seemed to rearrange itself into a deep three-dimensional picture, with the jets standing out from the rest further and further as they ran down the face. This whole built up a fascinatingly beautiful appearance as of a series of great flat moving icicles, the better part of a hundred metres long, standing out, by what looked like tens of metres at their points from the main sheet, like the overlapping, ruffled feathers of an angry cock.

My distance from the spillway was far too great for there to be any detectable difference between the images on my two retinas, and the clear subjective stereoscopic picture was evidently derived from the interpretation by an intermediate

level in my brain of the differential movement of the water masses.

The physical basis of the phenomenon can be understood in terms of common experience on a train journey. Looking out of the window, parallax causes the nearer objects to fall behind at a greater apparent rate than the farther ones. If one's own speed were known, this observation could give an accurate measure of distance away. Small birds, with their eyes on the sides of their heads, must use this effect to give them the accurate three-dimensional image of the world which is required for flying through bushes and trees, but of course we have no way of knowing what, if any, is the subjective effect as seen by a bird.

The face of the spillway filled enough of my field of view for my mind to interpret the relative motion of the parts, as it would have done if I had been moving and they at rest. This again is an effect familiar to railway travellers; when one is standing in a station and a neighbouring train starts to move, it is easy to feel convinced that it is one's own train that is moving.

I expounded this view as we walked away from the dam, and suddenly realized that if my explanation was true, this three-dimensional effect should be just as clear when using one eye as it was with two. So I dragged the others back and we all solemnly gazed at the face of the dam with one eye only (each). The subjective picture was exactly as it had been before. For a few moments the water looked flat, and then gradually the jets seemed to stand out until we were seeing exactly the same awe-inspiring set of vast overlapping and slowly moving sheets that we had seen before.

This observation seems to me worth reporting, not only for its beauty and novelty, but because it gives an extra datum on the handling of visual information by the brain.

It seems likely that the delay—familiar to stereoscopists in other non-standard circumstances—is due to the fact that the section of the brain responsible for presenting the final subjective picture concerns itself first with the differences between the data presented by the two eyes. If these differences are available, other clues are rejected—hence the success of a stereoscopic pair of pictures when we know perfectly well that we are looking at a pair of flat cards. If they are not available, other clues will be accepted, but the processing takes a little longer. Anyone who has lost one eye must be well aware of this, but I have never seen it discussed, and have never before been able to prove that the subjective image presented on the basis of motion parallax can be qualitatively identical with that derived from normal binocular vision.

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Do Membrane Filters prevent Cell Contacts?

MEMBRANE filters have been used by experimental embryologists and immunologists to separate tissue components and cell populations in experiments designed to distinguish between cell mediated communicative systems and soluble messengers. Most commonly, 'Millipore' filters have been used both in the construction of diffusion chambers¹ and in *in vitro* studies with isolated and recombined tissue components². Few systematic studies have been made into the completeness of separation and on the correlation between filter thickness and pore size with cytoplasmic ingrowth. Grobstein and Dalton³

have reported that 'Millipore' filters with an average pore size of 0.1 μm prevented virtually all cytoplasmic ingrowth. Most experimentalists have used 'Millipore' filters with even larger pores (0.45 μm to 0.8 μm) in the belief that they prevent cell contacts (see ref. 4).

Table 1 Pore Size of 'Nucleopore' Filters

Nominal pore size (μm)	Mean pore size $\pm$ s.d. (μm)
0.1	0.15 ± 0.02
0.2	0.20 ± 0.04
0.5	0.68 ± 0.06

Even by light microscopy cytoplasmic material may be seen in such pores, suggesting ingrowth of filaments. The depth of ingrowth, the nature of the material and the development of cytoplasmic contacts in the filters are difficult to investigate because 'Millipore' filters have a three-dimensional spongy structure with dead-end pockets and whirling pores^{5,6}. Also, the pore dimensions are variable within any given filter⁶. We report here studies with 'Nucleopore' filters which have cylindrical channels of even size and which have been used as a solid substrate for cultured cells⁷. 'Nucleopore' filters (General Electric Co., Vallecitos Nuclear Center, Pleasanton, California) with nominal pore sizes of 0.5, 0.2 and 0.1 μm respectively were used. The dimensions of the pores of different types of filters were determined from scanning electron micrographs by measuring the diameter of about 100 holes from enlarged negatives. Some slightly unexpected results were obtained (Table 1) as the pore mean size deviated from the nominal one.

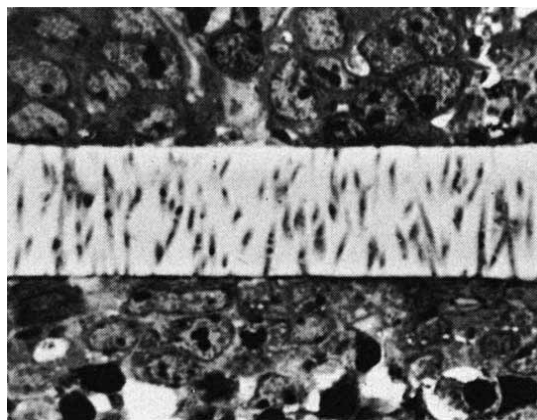


Fig. 1 Thick epon section of 48-h organ culture in which 'Nucleopore' filter with 0.5 μm pore size was used to separate mouse metanephric mesenchyme (above) from spinal cord tissue (below). A massive penetration of cytoplasmic processes from both tissues takes place in the filter. Toluidine blue staining. ($\times 1,500$.)

The experimental model system in which tissue separation was studied was a modification⁸ of that devised by Grobstein⁹. Metanephric mesenchyme and spinal cord dissected from 11-day mouse embryos were cemented with 1% agar on opposite sides of 'Nucleopore' filters. The results are based on observations made after 48 h cultivation of these explants. Cytoplasmic penetration into filters with nominal pore sizes of 0.5 and 0.2 μm could be seen by high-resolution light microscopy of 1 μm thick sections (Fig. 1). The processes filled the pores throughout the filter. Electron microscopy of these transfilter cultures showed that in filters with 0.5 and

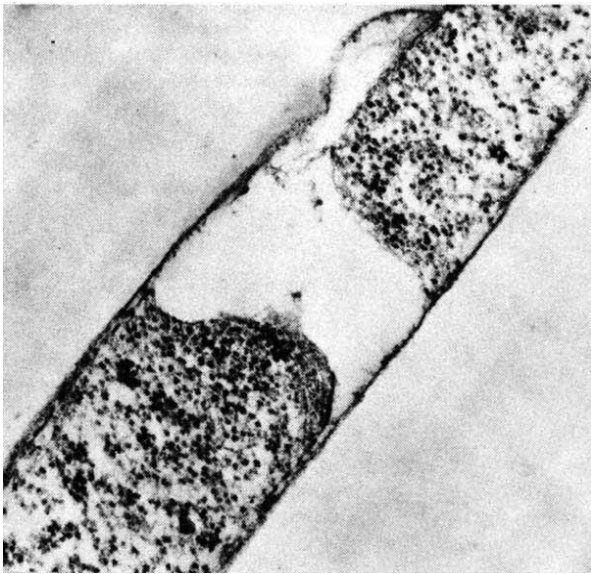


Fig. 2 Thin section of two cell processes in a 'Nucleopore' channel with 0.5 μm nominal diameter after 48 h organ culture as in Fig. 1. ($\times 30,000$.)

0.2 μm channels cytoplasmic processes extended from both tissues and made contact in the filter (Figs. 2 and 3). In those with 0.1 μm channels only occasional shallow ingrowth could be detected, with no transfilter cytoplasmic bridges.

Our observations show that cells can send long cytoplasmic processes into filters with pore diameters down to about 0.2 μm . Membrane filters do not therefore necessarily prevent contact between interacting cells, and extreme care should be taken in the interpretation of data obtained with interposition of such "barriers" between tissues; some of the older data may have to be re-evaluated. It is not clear whether our observations on the 'Nucleopore' filters are applicable to 'Millipore' type filters, which have a different pore structure. It should be emphasized that the filters used in this study were only 12 μm thick whereas the 'Millipore' filters are thicker. There must be a maximal distance over which cytoplasmic processes can extend and this is most likely a function of the pore size. Even in 25 μm thick 'Millipore' filters with a nominal pore size of 0.22 μm cytoplasmic material can be seen at all levels of the filter (our unpublished observation). Regular 150 μm thick 'Millipore' filters, however, probably prevent cell contacts. Our work shows the need for investigations to

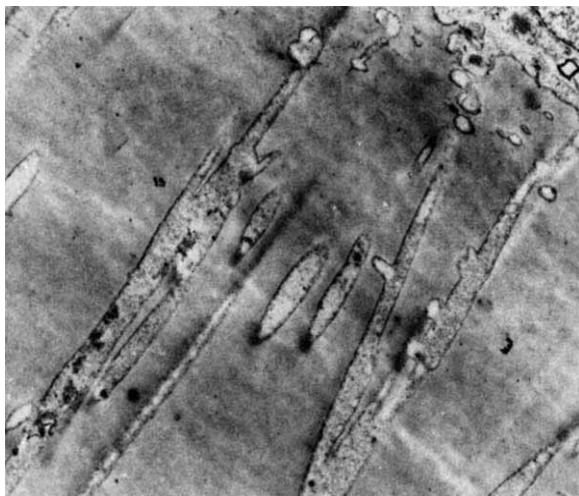


Fig. 3 Organ culture employing interposed 'Nucleopore' filter with 0.2 μm nominal pore size where cell processes are seen in the filter channels. ($\times 9,000$.)

get positive information about the non-existence of cell contacts permitting intercellular communications.

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Voluntary Control of Smooth Eye Movements and their Velocity

It has been shown recently that the eyes can make sustained smooth eye movements indistinguishable from normal pursuit movements in the absence of a moving visual stimulus if an after-image is tracked¹⁻³. This experimental procedure avoids the objections which can be raised against previous demonstrations of smooth eye movements without moving targets which have involved either alternative sources of information about movement⁴, or closing the eyes⁵, or changes in subjects' level of arousal⁶. But it has not yet been shown that smooth eye movements can be made voluntarily, and it is possible that they can be executed by alert, open-eyed subjects only if the saccadic system is inhibited by a visual target. This is a report on one subject, a 20-yr-old girl undergraduate, C. G., who can make smooth eye movements at will in the dark and can change the velocity of these movements on demand. These eye movements are indistinguishable from normal pursuit, do not resemble the eye movements made by the same subject when tracking an after-image, and seem, therefore, to represent specific voluntary control of the smooth pursuit eye movement system.

C. G. was tested twice in comparable conditions, with an interval of 5 months between experimental sessions. No qualitative differences were shown on the two occasions, so data from the second session only will be presented in detail here. (Relevant data for comparison from the first session are given in Table 1 in parentheses.) Horizontal eye movements were recorded by conventional electro-oculogram (EOG) techniques and the records permitted measurement of eye movements of 1° or more accurate to 1°. Head movements were controlled by a conventional chin-rest bite-bar assembly. The experiments were carried out in a special light-proof room. After a 10-min dark adaptation period the EOG was calibrated by a series of fixations to points 3°, 15° and 30° to the left and right of a central fixation point. The calibration was carried out in a dim red light. After calibration the red light was switched off and C. G. was instructed to make smooth movements during the first half of the experimental session, divided into six periods: (1) smooth eye movements at any velocity;

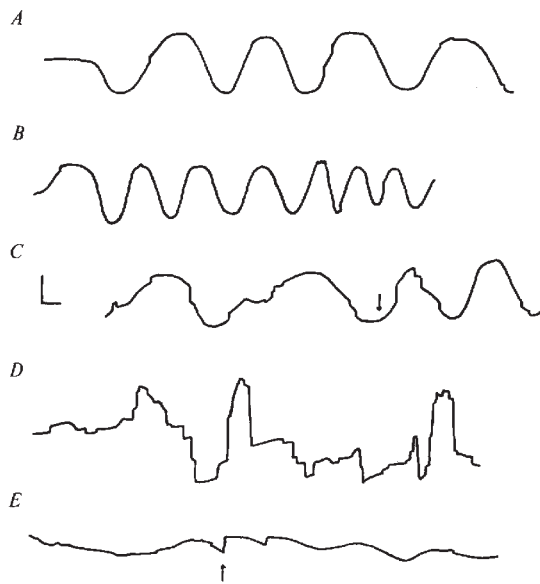


Fig. 1 Tracings of EOG recordings from C. G. A–C, Voluntary smooth movement, periods 1–4. The arrow in C is the transition point from periods 3 to 4. D, Attempts to make smooth eye movements with the eyes closed. E, Eye movements elicited by a foveal after-image. At the arrow attempts are made to move the after-image smoothly by moving the eyes. Leftward eye movements downward. Calibration: horizontal, 1.5 s; vertical, 30°.

In the second half, an extrafoveal after-image (1° diameter) was given 3° to the right of the centre of the fovea. Eye movements were recorded for one minute without any specific instructions being given before C. G. was asked to track the after-image.)

The results are given in Fig. 1 and in Table 1, which lists for each period the number, size and rate of saccades and the proportion of the total distance travelled in smooth movement by the eye. In all periods with the eyes open sustained smooth eye movements are made, interrupted by relatively few saccades (Fig. 1A–C). With the eyes closed, however, eye movements become saccadic (Fig. 1D) though these saccades are much slower and larger than those observed with the eyes open. Velocity changes, both increasing and decreasing, are shown in Fig. 1B and C; the arrow in Fig. 1C indicates the moment of transition from period 3 to period 4. Fig. 1E represents the eye movements elicited by a foveal after-image; at the arrow C. G. was asked to move the after-image smoothly by moving her eyes. These after-image-elicited movements do not resemble the voluntary smooth eye movements either in amplitude or velocity, and are slower and less extensive than those found under the same conditions in earlier studies^{1,2}. The overall mean rate of saccades is three times lower with a foveal after-image than in voluntary smooth eye movements, and the saccades themselves are smaller ($t=3.88$, $P<0.01$). When the eyes are closed, however, a foveal after-image actually increases the size of saccades ($t=2.08$, $P<0.05$) without affecting their rate. The proportion of the total distance travelled that is covered by smooth movement is not different in the voluntary smooth eye movements and the after-image conditions. This is in marked contrast to data from other

Table 1 Tracking Data showing Voluntary Control of Smooth Eye Movement

	Voluntary smooth movement						Foveal AI tracking	Move AI smoothly	Eyes shut with AI
	Period 1 own speed	Period 2 faster	Period 3 slower	Period 4 original speed	Period 5 eyes shut	Period 6 own speed			
Time (s)	43.5	36.5	24	30	36	33	84	60	36
No. of saccades	8	8	15	16	34	14	12	7	34
Rate of saccades (s ⁻¹)	0.18	0.22	0.62	0.53	0.94	0.53	0.14	0.12	0.94
Mean saccadic amplitude (°) (s.d.)	4.69 (1.94)	3.51 (1.99)	4.12 (3.4)	6.03 (2.34)	11.96 (14.26)	3.88 (1.94)	2.5 (2.2)	2.27 (1.61)	19.4 (16.7)
Net total distance of smooth movement (°)	520.05	622.18	174.3	391.69	320.21	292.33	129.31	150.86	252.9
Proportion of smooth movement (session 1 in parentheses)%	93 (96)	96 (86)	74 (78)	80 (81)	43	84	81	90	27
Mean velocity (° s ⁻¹)	13.34 (9.27)	23.75 (16.82)	12.4 (6.42)	15.47 (8.2)	—	10.86	—	—	—
Maximum velocity (° s ⁻¹)	30 (15.94)	50.41 (26.92)	17.34 (11)	22.75 (19.17)	—	20.41	—	—	—
Overall mean velocity	Periods 1–4: 13.01° s ⁻¹ (7.29° s ⁻¹)						1.55° s ⁻¹	2.52° s ⁻¹	

(2) smooth eye movements with an increased velocity; (3) smooth eye movements with decreased velocity; (4) smooth eye movements at the original velocity; (5) smooth eye movements with eyes closed; (6) smooth eye movements with eyes open again, at any velocity. The red light was then switched on and the EOG recalibrated. In the second half of the session, C. G. was given a 1° foveal after-image from a flashgun mounted behind the central fixation point. She was instructed to track the after-image if it moved; after 84 s she tried for a further 60 s to move the after-image smoothly with her eyes. A second period of attempting to make smooth eye movements with the eyes closed preceded the final calibration. (In the earlier experimental session only four periods were given in the first half, corresponding to the first four periods described above.

subjects attempting to make voluntary smooth eye movements in the dark (by tracking an imaginary pendulum) who show no significant smooth movement at all¹ and a saccadic rate of 1.72 s⁻¹.

Table 1 also shows maximum velocities (the mean for each period of the maximum slopes of each half-cycle of smooth eye movements) and mean velocities (the mean of the total amplitudes of each half-cycle divided by its duration) for the smooth eye movements in the different periods, as well as an overall mean velocity (net total distance of smooth eye movements divided by total time minus time taken for saccades) both for voluntary smooth eye movements and for after-image-induced smooth eye movements. Voluntary smooth eye movement again does not resemble after-image-induced smooth eye

movement on this measure; it seems therefore improbable that the voluntary movement is a product of tracking endoptic phenomena (which can produce smooth eye movement similar to that elicited by an after-image). Control of velocity is shown by the 68% increase in maximum velocity in period 2 and the 66% decrease in period 3. (Period 3 represents a 42% decrease in velocity compared with the original velocity of period 1.) An interesting asymmetry is apparent in maximum velocities to the left and to the right, speeds to the right averaging 18.43% less than those to the left. This asymmetry was also present in session one, where it averaged 24.48%. The attempt to match velocity in period 4 was less successful in the second experimental session than in the first, where mean velocities were matched between periods 1 and 4 to about 1° s^{-1} (Table 1). Voluntary control of pursuit velocity with a visual target has already been shown⁷.

In other subjects an extrafoveal after-image 3° from the fovea is a specific stimulus for saccades, such that, in the absence of instructions, a large number of small saccades are made away from the after-image and their mean amplitude is closely related to the retinal displacement of the after-image; in four subjects the mean rate of these saccades was $0.82/\text{s}$ (range: 0.52 s^{-1} – 1.03 s^{-1})². C. G., however, when tested in identical conditions in the first experimental session showed an almost complete suppression of saccades (rate: 0.06 s^{-1}) associated with almost complete immobility of the eyes apart from very slow, very limited, drifting. When instructions to track the after-image were given, eye movements similar to those of normal subjects were seen.

In attempting an explanation of foveal after-image tracking we suggested the importance of suppressing a neurologically distinct saccadic system in order to be able to use the pursuit (smooth) system. Such suppression is clearly shown in both after-image conditions to a marked extent by C. G. and (in comparison with other subjects) also during voluntary smooth eye movement. Saccadic interruptions do, however, become more frequent with time, and are more evident during slower smooth eye movements. Her ability to make smooth movement, and to change its velocity at will, reinforces the conclusion that the pursuit system does not require moving visual stimuli or any information about movement; nor does it require even the minimal visual information provided by an after-image. In some subjects at least, it is available as an independent voluntary system for moving the eyes.

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Cannibalism among Wild Chimpanzees

CANNIBALISM has been observed twice in East African chimpanzee populations. This behaviour is rarely seen among wild mammals and is hitherto unrecorded in non-human primates. It provides some basis for speculation

concerning the relationship between the predatory and aggressive behaviour of chimpanzees.

In both instances, a group of adult males somehow acquired an infant chimpanzee and began to eat it alive. On the first occasion, Suzuki¹ encountered the dominant male of his study population (in the Budongo Forest, Uganda) eating the flesh of a mutilated newborn infant. Other males showed great interest in touching and peering at the infant, which was apparently still alive. After 2 h the group departed from view, the dominant male still carrying the carcass.

I observed the second case of infant-eating at the Gombe National Park, Tanzania, in September 1971. I was following a small temporary association of habituated individuals who had for 3 h been feeding and resting, peacefully in riverine forest. Without apparent warning, they encountered two adult females, who had previously been silent. The older of the two was immediately and intensely attacked by the five adult males in my group. The female was an individual I had never seen in hundreds of hours of field observation, which suggests that it may also have been relatively unfamiliar to its attackers. I could not see whether or not it had an infant; its companion, a young female I had often seen before, had none.

The fighting mass of chimpanzees quickly disappeared into dense thickets, with continuous loud screaming. When I located them again, 2 min later, the strange female had disappeared and the males sat clustered in a tree, still calling. The dominant male, Humphrey, held a struggling infant about 1.5 yr old, which I did not recognize. Its nose was bleeding, as though from a blow, and Humphrey, holding the infant's legs, intermittently beat its head against a branch. After 3 min, he began to eat flesh from the thighs of the infant, which then stopped struggling and calling. The oldest male, Mike (aged 27–30, formerly the dominant male of the community but now low-ranking), approached and was permitted to tear off one of the infant's feet. All vocalizations had ceased by now, and the group descended to the ground, where I could observe them from 5 m or less.

Humphrey, a powerful mature male about 23 years old, remained in possession of the carcass for 1.5 h; meanwhile Mike sat close to him, eating the detached foot, and the three younger males (Figan, Jomeo and Satan, aged 18–14) watched intently but inertly. After half an hour, two females (who had been travelling with Humphrey's group before the kill) rejoined the males. Humphrey had by now stopped eating and was playing with the carcass, which was complete except for parts of the legs. In an exploratory manner, he peered, sniffed and poked at the carcass, groomed it, and often shook it by a leg or tapped its chest with his knuckles, such activities often increasing in intensity to culminate in violent punching, biting, or flailing the carcass against the ground. There were frequent lulls when Humphrey lay back and rested and the other individuals tentatively handled, groomed or nibbled the carcass, though if too persistent they were mildly threatened by Humphrey or Mike. Only the female Melissa, who was carrying her own year-old infant, made no attempt to investigate the carcass; in contrast, her juvenile son (aged 6) displayed great interest and ate small scraps of meat.

Eventually Humphrey walked away, leaving the carcass on the ground. Mike picked it up and the group dispersed. Mike ate meat slowly for 1.5 h and, unlike Humphrey, did not play with or groom the infant; he treated it solely as food. He abandoned it when Humphrey returned. Humphrey flailed the carcass against a rock, and left it, then Jomeo gnawed at it for 8 min. Mike returned with Humphrey, who took the infant forcibly from Jomeo: both tore off more meat, then departed with Jomeo, leaving the carcass with Figan and Satan, each of whom (respectively) kept the carcass for over 1 h. Each spent only a few minutes nibbling meat, and fed mainly on other foods

while holding the carcass. Figan (Fig. 1) played roughly with it, flailing and shaking, but Satan spent many minutes gently examining and grooming it. When Satan finally abandoned the infant, 6 h after the kill, only the legs, one hand, and the genital region had been eaten, although the carcass had changed hands six times. This suggests that the prey was less attractive as a food object, and more an object of curiosity, than other animals which Gombe chimps have been seen to eat. These include red colobus monkeys and the young of baboons, bushbuck and bushpig.



Fig. 1 Adult male "Figan" carrying the dead infant chimpanzee up a tree.

A detailed account of such predatory behaviour is in the press², but the general tendencies (drawn from 60 observations of meat-eating during the past 11 yr) are as follows. Prey individuals, weighing 5–20 pounds, are almost always caught singly by adult male bands whose members sometimes cooperate to isolate one monkey from its troop and to surround it. It is killed by biting or flailing, or dies while being dismembered. A successful capture releases intense excitement, but very little aggression, among the participants. Consumption of the carcass proceeds without delay, most meat being taken by mature males, and the carcass, if undivided, is usually retained by its captor, changes in ownership being rare. Vocalizations and begging interactions are usually frequent but exploratory or playful behaviour rare (the converse was true of the cannibals' behaviour) and no carcass has ever been seen to be abandoned incompletely eaten. Observations of meat-eating in the Budongo Forest¹ and the Kasakati Basin³ show close similarities to the Gombe data.

Predation on conspecifics is highly unusual among specialized predatory mammals; so also are amicable social interactions with a prey species, such as those which van Lawick-Goodall observed between chimpanzees and

baboons⁴ (though it should be noted that these involve mainly immature chimpanzees, who may have to learn which individuals in their social environment it is appropriate to interact with socially). The occurrence of both types of behaviour among chimpanzees suggests that chimpanzees have become predators so recently, or have practised predation at such a low level, that natural selection has not had time to eliminate such aberrations. In specialized social carnivores such as wolves, prey-killing may for long have been the sole means of obtaining food, social cooperation being a recent development which permits the capture of larger prey. Lorenz postulates⁵ that in such species, prey-killing and intraspecific aggression must be under independent motivational control. In chimpanzees, however, social organization (evolutionarily) probably preceded predation, which still seems strongly socially facilitated. Wild chimpanzees apparently ignore meat which they themselves have not killed, and adult males eat much more meat than adult females do; this suggests that predation is more than the fulfilment of a basic dietary need. Predatory behaviour is unlikely to have evolved from a herbivore's food-getting techniques; motivationally, it may overlap more with aggressive behaviour in chimpanzees than in specialized carnivores. Adult males are more aggressive than adult females; they sometimes stalk each other silently (as in prey-hunting) before an aggressive encounter and during "intimidatory" charging displays they often flail sticks with the same up-and-down motion sometimes used in prey-killing. Rarely, in this context, they may snatch up and briefly flail an unguarded infant in their path, usually without injuring it.

If chimpanzees have incorporated aggressive elements into predatory behaviour, the converse might conceivably occur, cannibalism arising from a situation of extreme aggressive arousal such as that preceding the Gombe infant-killing. If an infant were present who was not recognized as a member of their group, adult males might treat it less inhibitedly than a familiar infant; such may have been the case on that occasion.

The data are at present insufficient to indicate whether infant-eating in chimpanzees is aberrant behaviour, or a rarely-seen adaptive response to social or ecological pressures. Sugiyama⁶ observed that, in dense populations of langurs (*Presbytis entellus*), adult males sometimes killed all the infants in a troop on taking over its leadership, but the adaptive value, if any, of such behaviour is obscure.

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Phthalate Esters as Environmental Contaminants

We have found traces of phthalate esters in fish caught in various parts of North America. In a routine monitoring programme, gas-liquid chromatographic (GLC) analyses revealed

two unidentified peaks in many fish extracts and in procedural blanks examined for insecticide residues. The two compounds have now been identified with gas chromatograph-mass spectrometer techniques¹ as di-*n*-butyl and di-2-ethylhexyl phthalates. These compounds, widely used as plasticizers, proved to be of low toxicity, but our data suggest that they could be detrimental to some aquatic organisms.

Plasticizers are added to synthetic plastic resins to impart flexibility to the finished product, improve workability during fabrication and extend or modify properties not present in the original resins². Plastic formulations may contain up to 60 parts per hundred of plasticizers³. Phthalic acid esters are the most widely used plasticizers, particularly in polyvinyl chloride plastics. More than 800 million pounds of these plasticizers were produced in 1969³. Di-2-ethylhexyl and di-*n*-butyl phthalates are also used as an orchard acaricide and an insect repellent, respectively⁴. There is no well documented information on the fate of phthalate compounds in aquatic environments, nor have water quality criteria been established for them.

clean-up. The GLC column temperature was 155° C and the nitrogen carrier flow was 20 ml./min. The electron capture detector peak area response relative to an equal amount of DDT was 0.12 for di-*n*-butyl phthalate and 0.09 for di-2-ethylhexyl phthalate. The minimum detection limits for di-*n*-butyl and di-2-ethylhexyl phthalates were 0.1 and 0.5 µg/g, respectively. Various components of laboratory equipment, such as blender seals, disposable plastic gloves and plastic tubing, were found to be sources of phthalate ester contamination in residue samples. Reagent grade anhydrous sodium sulphate also contained some di-*n*-butyl phthalate and pre-washing with petroleum ether was required before use.

Standard static bioassay procedures were followed⁵ and acetone (0.7 ml./l.) was used as the solvent in evaluating phthalate ester toxicity. Mortality data were analysed by probit analysis⁶. Acute 96-h bioassays indicate that the toxicity of di-*n*-butyl phthalate to fish is relatively low (Table 2) compared with DDT (7–19 µg/l.). The 96-h TL₅₀ of di-*n*-butyl phthalate to scud (*Gammarus pseudolimnaeus*) was 2.1 mg/l. (DDT =

Table 1 Phthalate Ester, Polychlorinated Biphenyl and Insecticide Residues found in Selected Samples from North America

Source	Sample type	DNBP	DEHP	Residue (ng/g) PCB	Insecticide
Mississippi and Arkansas (agricultural and industrial areas)	Channel catfish	Trace	3,200	400	DDT-300 dieldrin-40, endrin-30, toxaphene-2200
Fairport National Fish Hatchery, Iowa (water supply from industrial area of Mississippi River)	Channel catfish	200	400	700	—
	Dragonfly naiads	200	200	200	—
	Tadpoles	500	300	1,000	Dieldrin-10
Black Bay, Lake Superior, Ontario (rural and industrial area)	Walleye	—	800	1,300	DDT-120
	Water	—	300	—	—
	Sediment	100	200	40	—
Hammond Bay, Lake Huron, Michigan (forested area)	Water	0.040	—	0.003	—
Lake Huron, Michigan	Water	—	5.0	0.20	—
Spirit Lake, Iowa (agricultural area)	Yellow perch	—	—	—	DDT-160, dieldrin-120, chlordane-30
Clover Leaf Lake, California (10,300 feet elevation)	Brook trout	—	—	—	DDT-110
Missouri River, McBaine, Missouri	Water (turbid)	0.09	4.9	0.20	—
Fish food and components	Commercial fish food	—	2,000 7,000	700 60	— DDT-30, dieldrin-60
	Casein	20	190	—	—
	Corn starch	20	170	80	—
	Gelatin	20	140	—	—
	Bone meal	30	400	—	—
	Wheat middlings	30	200	20	—
	Carboxymethyl cellulose	—	—	—	Chlordane-720

DNBP, di-*n*-butyl phthalate; DEHP, di-2-ethylhexyl phthalate.

*Residues approximated by 'Aroclor' 1,254 (80%), 1,248, and traces of 1,232.

†Residues presented for this group are the means of values for forty fish. Di-2-ethylhexyl phthalate residues ranged from 1,000 to 7,500 ng/g.

Phthalate esters were recovered from a 'Florisil' column in the 15% diethyl ether-petroleum ether eluate. The percentage recoveries for di-*n*-butyl and di-2-ethylhexyl phthalates were 90 and 50 respectively and the residue data in Table 1 are corrected values. The GLC retention time of the phthalate esters does not pose a significant interference problem in pesticide analyses. Retention times relative to aldrin were 1.24 and 14.9 for di-*n*-butyl and di-2-ethylhexyl phthalate esters, respectively. The GLC column used was a 1.8 m × 2 mm inner diameter packed with 80–100 mesh Corning GLC-110 glass beads coated with 0.3% OV-7. The retention time of methoxychlor relative to aldrin on this column was 11.9. A ⁶³Ni-electron capture detector served to establish residue levels after sample

1.0 µg/l.). The insolubility of di-2-ethylhexyl phthalate makes it difficult to evaluate the acute toxicity of this compound. However, fulvic acid, which occurs widely in soils and waters, has been shown to solubilize di-2-ethylhexyl phthalate⁷, and could possibly result in a greater availability of this compound to aquatic organisms.

Preliminary investigations indicate di-2-ethylhexyl phthalate is readily accumulated by fathead minnows (*Pimephales promelas*) continuously exposed to water containing 2.5 µg/l. phthalate, but residue concentrations in fish were only twenty-eight times that in the water after a 28-day exposure. However, we have found that scud will accumulate di-*n*-butyl and di-2-ethylhexyl phthalates 6,700 and 13,400 times the water con-

Table 2 Acute Toxicity of Di-*n*-butyl Phthalate to Four Species of Fish

Species	Temperature (°C)	TL ₅₀ * (µg/l.)		
		24 h	48 h	96 h
Fathead minnow (<i>Pimephales promelas</i>)	17	—	1,490	1,300
Bluegill (<i>Lepomis macrochirus</i>)	17	1,230	731	731
Channel catfish (<i>Ictalurus punctatus</i>)	17	3,720	2,910	2,910
Rainbow trout (<i>Salmo gairdneri</i>)	12	—	—	6,470

Toxicity was measured by standard static bioassay.

*The tolerance limit is the concentration in which 50% of fish survive for a specified time.

centration (0.1 µg/l.), respectively, within 14 days. Only 6% of residual di-2-ethylhexyl phthalate remained in the scud after 10 days in fresh water.

Di-2-ethylhexyl phthalate was examined for reproductive effects in zebra fish (*Brachydanio rerio*) and guppies (*Poecilia reticulata*) by dietary exposure. Zebra fish were fed diets containing 50 and 100 µg/g of food and guppies were fed 100 µg/g. Up to 88.5% of the zebra fish fry died before foraging began as compared with a 50% mortality in control fish. All the dying fry exposed to di-2-ethylhexyl phthalate died in tetany, which suggests that this compound may alter normal calcium metabolism. However, tetany did not occur in the dying controls. Intraperitoneal injections of di-2-ethylhexyl phthalate (3 µg/kg) increased serum calcium, decreased serum potassium, but did not affect serum sodium and chloride in coho salmon (*Oncorhynchus kisutch*). All of the adult guppies fed di-2-ethylhexyl phthalate became lethargic after 2 months of exposure and an 8% incidence of abortions was noted in this group. Continuous exposure of waterfleas (*Daphnia magna*) to 3 µg/l. of di-2-ethylhexyl phthalate significantly ($P < 0.05$) reduced reproduction by 60%. Details of these studies will be published separately.

The incidence of phthalate esters in fish seemed to be greater in aquatic areas associated with industrial and heavily populated regions, although hatchery and farmed fish fed diets contaminated with the esters also contained residues. Dietary contamination was probably a consequence of the use of contaminated fish products in feeds. Residues of phthalate esters previously reported in milk⁸ and bovine tissues^{9,10} may have resulted from dietary intake of phthalate esters. Phthalate esters have also been found in deep sea jellyfish¹¹ and soil¹². The actual amounts and distribution of these pollutants in the environment have not been fully investigated, but a recent report of 100 mg/l. phthalate esters in a water sample from the Ohio River, West Virginia, was not anticipated (R. Sandridge, personal communication).

The acute toxicity of phthalate esters seems relatively insignificant, but there are indications that these compounds can be detrimental to aquatic organisms at low chronic concentrations. They are produced in large amounts, they are in wide use as plasticizers, and, by some means, they are entering aquatic ecosystems. Thus, these compounds should be considered as environmental pollutants and a more detailed evaluation of toxicological effects of phthalate esters is essential to elucidate their impact on these systems.

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GENERAL

Will a Large Complex System be Stable?

Gardner and Ashby¹ have suggested that large complex systems which are assembled (connected) at random may be expected to be stable up to a certain critical level of connectance, and then, as this increases, to suddenly become unstable. Their conclusions were based on the trend of computer studies of systems with 4, 7 and 10 variables.

Here I complement Gardner and Ashby's work with an analytical investigation of such systems in the limit when the number of variables is large. The sharp transition from stability to instability which was the essential feature of their paper is confirmed, and I go further to see how this critical transition point scales with the number of variables n in the system, and with the average connectance C and interaction magnitude α between the various variables. The object is to clarify the relation between stability and complexity in ecological systems with many interacting species, and some conclusions bearing on this question are drawn from the model. But, just as in Gardner and Ashby's work, the formal development of the problem is a general one, and thus applies to the wide range of contexts spelled out by these authors.

Specifically, consider a system with n variables (in an ecological application these are the populations of the n interacting species) which in general may obey some quite nonlinear set of first-order differential equations. The stability of the possible equilibrium or time-independent configurations of such a system may be studied by Taylor-expanding in the neighbourhood of the equilibrium point, so that the stability of the possible equilibrium is characterized by the equation

$$dx/dt = Ax \quad (1)$$

Here in an ecological context x is the $n \times 1$ column vector of the disturbed populations x_j , and the $n \times n$ interaction matrix A has elements a_{jk} which characterize the effect of species k on species j near equilibrium^{2,3}. A diagram of the trophic web immediately determines which a_{jk} are zero (no web link), and the type of interaction determines the sign and magnitude of a_{jk} .

Following Gardner and Ashby, suppose that each of the n species would by itself have a density dependent or otherwise stabilized form, so that if disturbed from equilibrium it would return with some characteristic damping time. To set a time-scale, these damping times are all chosen to be unity: $a_{jj} = -1$. Next the interactions are "switched on", and it is assumed that each such interaction element is equally likely to be positive or negative, having an absolute magnitude chosen

from some statistical distribution. That is, each of these matrix elements is assigned from a distribution of random numbers, and this distribution has mean value zero and mean square value α . (For a fuller account of such a formulation, see refs. 2 and 3.) α may be thought of as expressing the average interaction "strength", which average is for simplicity common to all interactions. In short,

$$\mathbf{A} = \mathbf{B} - \mathbf{I} \quad (2)$$

where $\mathbf{B}$ is a random matrix, and $\mathbf{I}$ the unit matrix. Thus we have an unbounded ensemble of models, one for each specific choice of the interaction matrix elements drawn individually from the random number distribution.

It is important to note that randomness only enters in the initial choice of the coefficients a_{jk} , which then define a particular model. Once the dice have been rolled to get a specific system, the subsequent analysis is purely deterministic.

The system (1) is stable if, and only if, all the eigenvalues of $\mathbf{A}$ have negative real parts. For a specified system size n and average interaction strength α , it may be asked what is the probability $P(n, \alpha)$ that a particular matrix drawn from the ensemble will correspond to a stable system. For large n , analytic techniques developed for treating large random matrices may be used to show* that such a matrix will be almost certainly stable ($P \rightarrow 1$) if

$$\alpha < (n)^{-1/2} \quad (3)$$

and almost certainly unstable ($P \rightarrow 0$) if

$$\alpha > (n)^{-1/2} \quad (4)$$

The transition from stability to instability as α increases from the regime (3) into the regime (4) is very sharp for $n \gg 1$; indeed the relative width of the transition region scales as $n^{-2/3}$.

Such a precise answer for any model in the ensemble in the limit $n \gg 1$ is a consequence of the familiar statistical fact that, although individual matrix elements are liable to have any value, by the time one has an $n \times n$ matrix with n^2 such statistical elements, the total system has relatively well defined properties.

Next we introduce Gardner and Ashby's connectance, C , which expresses the probability that any pair of species will interact. It is measured as the percentage of non-zero elements in the matrix, or as the ratio of actual links to topologically possible links in the trophic web. The matrix elements in $\mathbf{B}$ now either, with probability C , are drawn from the previous random number distribution, or, with probability $1 - C$, are zero. Thus each member of the ensemble of matrices $\mathbf{A}$ corresponds to a system of individually stable parts, connected so that each part is affected directly by a fraction C of the other parts. For large n , $\alpha^2 C$ plays the role previously played by α^2 , and we find the system (1) is almost certainly stable ($P(n, \alpha, C) \rightarrow 1$) if

$$\alpha < (nC)^{-1/2} \quad (5)$$

and almost certainly unstable ($P \rightarrow 0$) if

$$\alpha > (nC)^{-1/2} \quad (6)$$

* From equation (2) it is obvious that the eigenvalues of $\mathbf{A}$ are $\lambda - 1$, where λ are those of $\mathbf{B}$. The "semi-circle law" distribution for the eigenvalues of a particular random matrix ensemble was first obtained by Wigner⁴, and subsequently generalized by him to a very wide class of random matrices whose elements all have the same mean square value⁵. Although the matrix $\mathbf{B}$ does not in general possess the hermiticity property required for most of these results to be directly applicable, the present results for the largest eigenvalue and its neighbourhood can be obtained by using Wigner's⁴ original style of argument on $(\mathbf{B}^N)(\mathbf{B}^N)^*$ where N is very large. Indirectly relevant is Mehta⁵ and Ginibre⁶.

It is interesting to compare the analytical results with Gardner and Ashby's computer results for smallish n . (Their choice of $\mathbf{A}$ differs slightly from ours, but in essence they have the fixed value $\alpha^2 = 1/3$, and diagonal elements intrinsically -0.55 rather than -1 .) Although our methods are based on the assumption that n is large, and are therefore only approximations when applied to $n=4, 7, 10$, the two approaches in fact agree well when compared, being not more than 30% discrepant even for $n=4$.

The central feature of the above results for large systems is the very sharp transition from stable to unstable behaviour as the complexity (as measured by the connectance and the average interaction strength) exceeds a critical value. This accords with Gardner and Ashby's conjecture.

Applied in an ecological context, this ensemble of very general mathematical models of multi-species communities, in which the population of each species would by itself be stable, displays the property that too rich a web connectance (too large a C) or too large an average interaction strength (too large an α) leads to instability. The larger the number of species, the more pronounced the effect.

Two corollaries are worth noting, although they should not be taken to have more than qualitative significance.

First, notice that two different systems of this kind, with average interaction strengths and connectances α_1, C_1 and α_2, C_2 respectively, have similar stability character if

$$\alpha_1^2 C_1 \approx \alpha_2^2 C_2 \quad (7)$$

Roughly speaking, this suggests that within a web species which interact with many others (large C) should do so weakly (small α), and conversely those which interact strongly should do so with but a few species. This is indeed a tendency in many natural ecosystems, as noted, for example, by Margalef⁷: "From empirical evidence it seems that species that interact feebly with others do so with a great number of other species. Conversely, species with strong interactions are often part of a system with a small number of species. . . ."

A second feature of the models may be illustrated by using Gardner and Ashby's computations (which are for a particular α) to see, for example, that 12-species communities with 15% connectance have probability essentially zero of being stable, whereas if the interactions be organized into three separate 4×4 blocks of 4-species communities, each with a consequent 45% connectance, the "organized" 12-species models will be stable with probability 35%. That is, of the infinite ensemble of these particular 12-species models, essentially none of the general ones are stable, whereas 35% of those arranged into three "blocks" are stable. Such examples suggest that our model multi-species communities, for given average interaction strength and web connectance, will do better if the interactions tend to be arranged in "blocks"—again a feature observed in many natural ecosystems.

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BOOK REVIEWS

Faraday's Letters

The Selected Correspondence of Michael Faraday. Edited by L. Pearce Williams with the assistance of Rosemary Fitzgerald and Oliver Stallybrass. Vol. 1. 1812-1848. Pp. xiii+1-538. Vol. 2. 1849-1866. Pp. viii+539-1079. (Cambridge University: London, December 1971.) £21.00; \$55 the set.

HISTORIANS of science, whether amateur or professional, must be grateful to the Royal Institution, who in the 1930s gave us an edition of Faraday's *Diary*—really his laboratory notebook—and have now complemented it with this selection of his correspondence. These 814 letters—mostly previously unpublished—are a curious collection. About half were written to Faraday, and about half by him; but unfortunately we do not very often find both sides of a correspondence complete. When we do, as with Whewell and de la Rive, the result is a splendid picture of two great minds working upon one another; the incomplete correspondences are sometimes frustrating. Some of the letters are private, though often concerned with science, while others were written for the public and were either addressed directly to the editor of a journal or sent to Faraday for him to publish as he saw fit. The great question which we shall want to ask is what light these letters cast upon Faraday's life and times; and though the light may sometimes be fitful, many aspects of the science of the nineteenth century are illuminated.

We see Faraday first as a chemist, beginning his scientific training under Davy; and it is worth noticing that in the British Association, Faraday only held office in the chemical section. His charming letters to his friend Abbott describe his experiments, most dramatically with the explosive nitrogen trichloride in a laboratory where no safety precautions were taken. We can follow him on his tour of the Continent with Davy at the end of the Napoleonic Wars, and then at the Royal Institution working on the liquefaction of gases and the analysis of gas-oil.

By the 1820s he had established a reputation, and had several foreign correspondents; and we can begin to follow his work on electricity. He had never been happy about the atomic theory in chemistry, and we find him from the first sceptical about Ampère's theory of electromagnetism, although admitting that it worked. We see him involved in priority disputes, and gradually developing his ideas and his nomenclature, particularly in correspondence with Whewell. Gradually he becomes more explicit about his lines of force, and we find William Thomson and Clerk Maxwell developing mathematical means of expressing his insights. We find also his work on diamagnetism, and his interest in terrestrial magnetism which fills several letters in his correspondence with Airy, the Astronomer Royal, who consulted Faraday over numerous questions.

We also find Faraday engaged in applied science; making glass of very high refractive index, analysing and making steels, and advising about telegraphs. He had to give his opinion on a proposal to attack Cronstedt with sulphur-filled fireships to smoke the defenders out, and he performed experiments to investigate food adulteration and water pollution. At the very end of his working life he was actively concerned with the improvement of lighthouses, and there are many letters connected with these researches.

Throughout his career Faraday worked at the Royal Institution, and there are many letters relating to this great centre of research and lecturing. Sometimes he complains about the time that administration and "commonplace employment" takes, but he clearly enjoyed lecturing and some of the letters contain useful advice to lecturers. He informs a correspondent that he does not need a grant for apparatus, because he is sure that the members of the Royal Institution would raise one or two thousand pounds for him if he asked for it.

The letters also cast much light on Faraday as a man. He begins as a very attractive and eager youngster, who

turns into a young man who is both proud and humble, keeping his end up firmly in priority disputes; we see him acting in old age as a peacemaker. We see his breakdown and recovery and his peaceful old age. We find him refusing all invitations to dine, refusing office in the Royal Society, refusing testimonials even to those of whose work he had a high opinion, and avoiding occasions such as British Association meetings as far as possible. His strong religious faith is very evident. As a scientist, we see him sceptical—as were many chemists of his day—about a purely theoretical paper, and about an attempt to learn science from books rather than in the laboratory; and we find him repeatedly regretting his ignorance of German and his inability to learn it. We also find him fixing up a job in India for Liebig's son, and asking Liebig to look after his nephew.

It is not surprising to find Faraday sceptical of applied mathematicians; but there are some surprises in the correspondence. Faraday heard very late the anecdote of Oersted's great discovery as coming out of a lecture-demonstration; Plücker complained that as a poor German professor he had little time to do experiments; and Joseph Henry wished that the Smithsonian could have been in a building more like the Crystal Palace. Faraday makes some amusing remarks, like some modern philosophers of science, about scientists' distaste for novel discoveries; and deplores the involvement of scientists in politics. He was averse to honours, though prepared to accept them from foreign governments; but he wished that the British Government would institute honours especially for men of science.

The editorial material is brief, sometimes indeed almost telegraphic, but is generally accurate; it is a pity that in the headings to letters 446 and 448 a new member has been added to the illustrious Becquerel family by the incorporation of M., for Monsieur, as though it were an initial, and that the note to 602 refers us to the wrong lecture.

DAVID KNIGHT

Colonial Science

Science in the British Colonies of America. By Raymond P. Stearns. Pp. xx+760. (University of Illinois: Urbana, Chicago and London, 1970.) \$20.

By drawing together a mass of well documented material on the activities of natural philosophers in North America from the sixteenth century to the Revolutionary wars, R. P. Stearns has materially extended our knowledge, and his book is a valuable addition to the reference shelf. Firmly based on the manuscript materials relating to the subject in the Bodleian library, the British Museum and the Royal Society, as well as those contained in several American learned institutions, the book combines these with an examination of the printed works of the men whose careers it relates. It thus amply fulfils Stearns's stated objective, the provision of "a comprehensive overview of the scientific interests and activities of American colonials". The approach is largely biographical, short accounts being given of individuals grouped together in geographical regions. Inevitably this makes for somewhat unexciting reading, but Stearns does attempt to pull his work together with introductory and concluding commentaries, and by occasionally standing back to analyse and assess the factual evidence that he presents. In addition to the main text, five sets of "queries", drawn up by the Royal Society in the hope that travellers to America in the 1670s would bring back answers, are usefully printed in the appendices, together with a checklist of colonial fellows of the Royal Society. A discussion of the location of manuscripts with some indications of areas for future research and a competent index complete the work. Inevitably in a book of this size there are several minor errors. Two which might be corrected in a future edition are the fictitious knighthood conferred on Robert Boyle, and the date of the *Musaeum Tradescantium*, 1656, not 1658. It should also be noted that there is evidence that this catalogue was largely written by Elias Ashmole and Thomas Wharton in 1652, and not solely by John Tradescant as stated by Stearns.

The usefulness of this book is out of doubt, but of its historical validity one is less certain. Although Stearns acknowledges the foolishness of applying twentieth century criteria of "science" to the seventeenth and eighteenth centuries, he tends none the less to do so and is by so much distanced from his subject matter. Particularly is this true of his treatment of colonial "promotional literature", and of the sixteenth century. Thus the statement "scholars had become so

excited in incorporating into the old science [referring primarily to botany and zoology] the new products that captured their notice that they gave too little attention to problems of natural science as a whole" is meaningless because the men to whom Stearns refers had no conception of a dichotomy such as is here postulated, but were carrying out with the new materials such operations as the intellectual and social nexus in which they worked required. Doubts also arise about other parts of Stearns's interpretation. Although he is able to display rather more activity on the part of the Royal Society than might have been expected, his failure to distinguish between the work of the Society as a whole, and the individual efforts of its members, calls into question Stearns's whole reading of the structure of English science in the seventeenth century. Moreover one might question the underlying assumption that natural philosophy in the colonies was, almost by definition, less sophisticated than that in England and Europe. Reading his account one is struck by the similarities displayed with natural philosophy in the English provinces. The complaints of isolation made by a John Winthrop in the New World can be paralleled with those of a John Beale in Somerset (who made proposals to rectify the situation) or the comments of a George Garden in Scotland. Indeed in many ways the colonists attracted more attention, because of the novelties of their environment, than naturalists in the English provinces. Moreover while the Royal Society was prepared to waive colonial subscriptions, the English provincial, who might effectively be as isolated as his colonial counterpart, received no such benefit. Although Stearns insists that American science should be studied in relation to that of England and Europe, he has perhaps not recognized what are the appropriate relations, and has thus exaggerated American isolation during the earlier part of the period. It is unfortunate that at many other points in the argument, similar doubts and objections arise. Valuable though Stearns's work is for reference, it is not a satisfying piece of historical writing.

A. J. TURNER.

Details of Development

Lectures on Developmental Physiology. By Alfred Kühn. Translated by Roger Milkman. Pp. xv+535. (Springer: Berlin and New York; Universal Book Stall: New Delhi, 1971.) 68 DM; \$21.20.

THE late Alfred Kühn, a distinguished zoologist, published the second and final edition of this book in 1965, and Roger Milkman has performed the Herculean

task of translating it into English. It is a set of thirty-six lectures: the first five contain a review of classical cytology; the next five are on the development of lower organisms, including a chapter on fertilization; eleven chapters are on experimental embryology; four chapters are on insect development; four on plant development; two on regeneration, and the concluding five chapters are on a mixture of general principles of development and gene action.

This book is literally what it claims to be: a series of lectures. It is not a tightly constructed book taking a point of view, nor is it an analysis of development. It is a detailed and comprehensive review of selected morphological and experimental studies of the development of a large variety of organisms. The difficulty is that Professor Kühn has done this by writing extensive descriptive passages which make for very hard and certainly dull reading. On the other hand, the 620 illustrations are excellent and tell their story effectively.

As far as I could judge the sections on animal embryology, and especially all the discussion of insect development, are accurate and comprehensive. The parts on plant development are somewhat spotty in their coverage, while the short section on cellular slime moulds is unfortunately full of errors. Another serious problem is that the book is about 10 years old in its content. This means that much of the interesting recent work in many areas is lacking.

Yet despite all these criticisms, this is an impressive book. Many sections will be useful to advanced students; it is a large survey of some of the important work in developmental biology of the first half of this century. The organisms and the experiments he describes must not be forgotten; it is only a pity that their relevance to modern developmental biology has not been made clearer.

J. T. BONNER

Mites

The Oribatid Genera of the World. By J. Balogh. Pp. 188+71 plates. (Akademiai Kiado: Budapest, 1972.) £5.

ORIBATID mites represent one of the commonest groups of arthropods in soil and leaf litter. More than 130 families and 700 genera have been described and, undoubtedly, many new forms await discovery. During the past decade the rate at which new taxa have been described has surprised even the specialists, and there is an urgent need for the comprehensive taxonomic review now provided by Dr Balogh.

The task that Dr Balogh has set himself is one from which most taxonomists

would recoil, for many oribatid genera have been described uncritically. In presenting a catalogue of families and genera, and identification keys, Balogh has considered "every hitherto described family and genus (as) distinct" and synonymies, except the more obvious ones, have been ignored. This is bound to confuse "nonspecialist soil zoologists" for whom these keys are intended. The terminology used in the keys is straightforward and the author has taken pains to explain many of the technical terms, although the inclusion of a brief discussion of basic leg chaetotaxy would have been helpful. Identification keys are accompanied by code tables in which groups of similar genera are defined such that a genus may be distinguished from others in its group by simple comparison of certain quantitative features. These tables provide useful checks when used in conjunction with the keys, but the nomenclature devised to delimit the generic groupings will daunt the beginner. The illustrations, of which there are over a thousand, have been prepared to a standardized format and more than adequately complement the text.

There are avoidable errors, a few species wrongly attributed, and a disturbing tendency to introduce new family and genus names without any explanation. But the specialist will willingly live with these shortcomings in exchange for the wealth of information contained in this invaluable book.

JOHN A. WALLWORK

Probability in Science

Scientific Truth and Statistical Method. By Marcello Boldrini. Translated from the Italian by Ruth Kendall. Pp. xiv + 264. (Charles Griffin: London, January 1972.) £5.40.

THE philosophy of science is a notoriously unsatisfactory subject in the eyes of most scientists, for it neither portrays with accuracy how they argue, nor prescribes with conviction how they ought to argue. It is, in consequence, usually neglected by them, with the result that it becomes even more detached from the reality of scientific investigation.

It might have been supposed that the introduction of probabilistic reasoning in the eighteenth century would have provided the missing clue, but in fact it has greatly added to the richness of the discussion without bringing it perceptibly closer to a conclusion.

Some philosophers of science have neglected probability altogether, and only one, Dr Hacking in his *Logic of Statistical Inference*, has made a successful excursion into the real world of statisticians.

Professor Boldrini's work, now happily translated into English, suffers the disadvantage of having been written before Dr Hacking's was published in 1965. But the fields covered by the two books are more different than their titles suggest, Professor Boldrini's being less concerned with statistical method than scientific truth, and ranging widely over the whole of the philosophy of science. Indeed, at times it becomes a rather disconnected ramble round the celebrated names of the subject, with the attendant pleasure of a close examination of the wayside flowers tending to conceal the lack of progress in any particular direction.

The book is in five sections, "Science and Language", "Axioms", "Deduction and Induction", "Probability and Statistics", and "The Methodological Structure of the Natural Sciences".

There is no detailed discussion of the different points of view that continue to divide the statistical world, Professor Boldrini seeming somewhat reluctant to descend from the distant contemplation of theories of probability to the practical question of the validity of common statistical procedures. The basic rift between Bayesians and non-Bayesians, which goes right to the bottom of the discussion on scientific truth and statistical method, is not given the importance it deserves, and Ramsey's work is nowhere mentioned. Professor Boldrini decides for himself "in a non-Bayesian sense", following which one might have expected a discussion of the differences between Fisher and the school of Neyman and Pearson, but there is no inkling that any such differences exist.

Most extraordinary is the absence of any evidence that the author was aware of the existence of Fisher's book *Statistical Methods and Scientific Inference*, published in 1956, in spite of the fact that he recommends Fisher and Karl Pearson as "eminent examples of original minds, from whom every statistician should draw inspiration". Perhaps, like Professor M. G. Kendall, he wished the book had never been written, or, like Professor D. V. Lindley, he found it a disappointment. We should like to have known.

A. W. F. EDWARDS

Live Ancient Monuments

Crocodiles: Their Natural History. By C. A. W. Guggisberg. Pp. x + 195. (David and Charles: Newton Abbot, March 1972.) £2.75.

CROCODILIANS do not attract much attention outside specialist circles, so I had not expected to see two general works on them appear within months of one another—the other is by Wilfred T.

Neill. Mr Guggisberg's work is more directly aimed at interesting the public and making a plea for conservation.

The twenty-two or so living species of crocodilians are described and their ranges indicated. There is a general account of the principal features of crocodilians and their evolution. The work is evidently addressed to non-technical readers, and I wonder what they will make of such features as the figure of an alligator's brain with no particular relevance to the text or of the "considerable antero-posterior expansion" of the ilium.

The author is evidently very well read on crocodile lore. There are many interesting stories including numerous personal observations, mostly on the Nile crocodile. Some of these stories Neill regards as mythical—as, for example, that they knock down their prey with their tails and that old gharials have a swelling on the end of the snout. In this latter case, however, Guggisberg gives us a reference to a published photograph. In considering crocodiles as a hazard to human life Guggisberg concludes that a large proportion of accidents is due to the extraordinary nonchalance of people who live near crocodile infested waters. The author argues that a really serious threat to their survival has developed only recently as a result of a fashion for the leather. Conservation is discussed—I liked the suggestion that we should preserve crocodilians as one of the world's most ancient monuments.

GARTH UNDERWOOD

Early Earth Science

Earth Sciences. (The Royal Institution Library of Science, being the Friday Evening Discourses in Physical Science held at the Royal Institution 1851–1937). Edited by Stanley Keith Run-corn. Vol. 1: Pp. xx + 502. Vol. 2: Pp. xvi + 539. Vol. 3: Pp. xvi + 499. (Applied Science: London, 1971.) £20 the three volumes.

THIS three-volume work, totalling about 1,500 pages, presents a record of 135 Friday Evening Discourses delivered at the Royal Institution from 1851 to 1937, on a particular group of subjects, the so-called Earth sciences. This term is now in use to include a number of specialized branches of science formerly comprised under the less cumbersome and equally comprehensive term geology. A rough breakdown of the subjects of the lectures shows that about eighty are likely to be of particular interest to geologists; thirty are on meteorology; a few are on oceanography, travel and exploration; and there are a small number on subjects that do not fall readily into any of these categories. In some

lectures there is an overlap of interest. Thus, the editor has cast his net fairly widely.

Evening Discourses had been delivered before 1851, but it was only from this year, in which the first volume of the *Proceedings of the Royal Institution* appeared, that it became the custom to publish them. They have now been reproduced, together with the illustrations, exactly as they were printed in these *Proceedings*. These versions are, presumably, those submitted by the lecturers for publication, some being in summary form, others of considerable length.

In general the lectures were given by men who were masters of their subject, or, at least, had something new to say; and the lectures were intended for the intelligent public rather than for specialists. Specialists were not excluded from the audiences, however, so that the lecturers had the difficult task of pleasing a mixed gathering, as some contemporary comments show.

Thus, the geologist A. C. Ramsay once wrote that "The Royal Institution is the most ticklish audience in Britain to lecture before, because the most critical and refined, and possessing also, in large and equal shares, so much knowledge and so much ignorance".

In 1856 T. H. Huxley made a similar comment, in allusion to a criticism of the Royal Institution lecture audiences made by the palaeontologist Hugh Falconer. He wrote that "The Friday evening audience at the RI [is] one which the best men in the country approach gravely and earnestly, knowing as they do that whatever the 'mixture' of their hearers there is pretty sure to be among them a fair jury of their peers".

On the other hand, another geologist, Gideon Mantell, referring to a lecture by Sir Roderick Murchison on the Alps (reproduced in this work), stated that "his illustrations were beautiful, but the discourse a very indifferent one: the room crowded with the elite of fashionable lady and gentleman science-fanciers". Mantell's reflexion on the quality of this discourse may perhaps refer to the fact that Murchison's explanation of the origin of the Alps was by then somewhat outdated. The nature of the audiences at these lectures must, nevertheless, have ensured that they were scientifically of a high standard and that accuracy was not sacrificed to gain popular esteem. Taken as a whole they reflect the growth of knowledge in a period during which science as a whole, and particularly geological science, was expanding rapidly.

In the mid-nineteenth century interest in both geology and meteorology was considerable. The early years of the century had seen the birth of geology as a modern science and during the

subsequent period of rapid growth it attracted the attention of other scientists, notably biologists and physicists, as well as considerable popular attention. Thus, it is not surprising that among the earlier Evening Discourses as many as twenty-four on geology were delivered in the decade 1851-1860, and about one every year until 1890. Thereafter there was a gradual falling off in the number of geological lectures. From 1899 to 1937 only twelve were given. The new and startling developments in physics and chemistry, the discovery of X-rays, of the radioactive elements and of isotopes, probably diverted attention from geology.

Interest in meteorology was also considerable during the nineteenth century, for the British Meteorological Society was founded in 1850, the Scottish Meteorological Society in 1855, and in the latter year also a Meteorological Department was established within the Board of Trade. In Great Britain, contrary to the practice in the USA, meteorology is not regarded as one of the Earth sciences. The only obvious connexion between the two is that various manifestations of the weather, the action of rain, water, ice and wind on rocks, are of interest to geologists in determining the conditions under which particular deposits were formed in past geological ages. Thus, it is the meteorologist who turns to the geologist, rather than vice versa, for information on palaeoclimatology. This link between the two sciences is exemplified in two lectures; but for the most part the meteorological discourses have little bearing on geology, though they are probably of interest to physicists and chemists.

Many well known names appear among the lecturers represented in these volumes. Others are almost forgotten, and one or two are quite unexpected, such as that of John Ruskin, who was responsible for two geological lectures, in one of which, on Verona and its rivers, he diverges into architecture and Italian history, and finishes up with the plea, "It has now become a most grave object with me to get some of the great pictures of the Italian schools into England".

Among the well known names John Tyndall was responsible for seven lectures, some on geology and others on glaciology; Sir Charles Lyell and Sir Andrew Ramsay each lectured five times, and Sir Archibald Geikie gave two lectures. T. H. Huxley lectured on the work of the Challenger expedition, and its bearing on geological problems. William Pengelly, a Devonshire schoolmaster, gave four lectures, two of which relate to the excavations in Kent's Cavern and Brixham Cave, in which human artefacts had been found in association with the bones of extinct

animals. This discovery, with which Pengelly was closely associated, played a major part in persuading a then sceptical scientific world to accept the contemporaneity of man and extinct animals. In one of Ramsay's lectures, given in 1857, he discussed his claim, first made in 1854, and based on evidence from the Welsh borderland, that an ice age had existed in England in Permian times. This was the suggestion of an imaginative man, but he must have required some temerity to put it forward at a time when even the former existence, and extent, of the Pleistocene ice sheet was still not universally believed. He can hardly have been surprised that his claim was not accepted readily, and lamented the fact at a geological dinner party in 1856:

"Few, few believe what I have told
Men say that I am overbold.
What then? they sneered that Welshmen's
tails
Had polished Buckland's rocks in Wales.

And when I'm dead, and these poor bones
Lie underneath the turf and stones,
The home of worms and churchyard mice,
Men then will swallow Permian ice."

The latter prophecy has since proved correct, though not as far as this country is concerned. Though Ramsay was a great field geologist, in this instance his evidence proved to be unsound.

The post-1900 lectures include R. J. Strutt on "Radioactive Changes in the Earth"; John Joly on "The Age of the Earth", in which he compares the results obtained by geological evidence with those obtained by the then new radioactive methods; W. L. Bragg on "The Structure of Silicates", in which he demonstrated the great advance in knowledge of crystal structure that had been obtained by the use of X-rays; and V. M. Goldschmidt of Copenhagen on the "Distribution of the Chemical Elements".

Among those who lectured on meteorology were Faraday on "Atmospheric Magnetism"; William Thomson on "Atmospheric Electricity"; the American astronomer and expert on aeronautics, S. P. Langley, on "The Earth's Atmosphere"; Sir Napier Shaw on "Modern Weather Forecasting"; and Sir James Dewar on "Cloud Studies".

Many branches of geology are dealt with in these lectures, as well as various aspects of meteorology; and an extensive index adds to the value of the work. As a whole, it ought to prove useful to readers interested in the advancement of science during the period covered, and there is much to interest the general reader. For those fortunate enough to possess a copy, it might be looked on as an armchair or bedside book, to be dipped into at leisure, though its price suggests that consultation will usually have to be made in a library.

V. A. EYLES

Not Just Guinea-pigs

The Laboratory Animal—Principles and Practice. By W. Lane-Petter and A. E. G. Pearson. Pp. xi+293. (Academic: New York and London, December 1971.) £4; \$11.50.

Laboratory Animals: An Annotated Bibliography of Informational Resources Covering Medical Science (Including Husbandry Technology). Edited by Jules S. Cass. Pp. iv+250+60. (Hafner: New York; Collier-Macmillan: London, April 1972.) £6.75.

The Laboratory Animal is an attractive, well produced volume containing eleven chapters on the principles and practices of laboratory animal science. Although most of the contents are familiar, the authors have presented the material in a new and interesting manner. For example, the chapter on utilization is really a delightfully phrased psychological analysis of a scientific investigator and his reasons for choosing a particular species of animal.

The chapters on sources and trends refer to available supplies and species likely to be in demand in the foreseeable future. This section throws new light on both scientific and philosophical problems, in particular those associated with stray dogs and cats and the destruction of more animals each year than are needed by scientists. Some practical suggestions for the guidance of those seeking to supply collected dogs and cats or those wishing to use them may be ill received as a growing number of scientists and animal welfare people advocate that only specially bred animals should be used for research. The increase in the use of invertebrate animals in the UK is presented in a bold and unbiased manner. The authors clearly state the numbers of animals used from 1935 to 1970 and the uses to which they have been put. This information may well provide material for persons wishing to oppose the use of living animals in scientific research. On the other hand, substitutes for laboratory animals are given equal prominence, and attention is drawn to the advances made in this field. However, there will always be a need to investigate response in the complete living animal.

The chapter on genetics is not up to purists' standards but it does contain good basic facts which are well presented and of immense value to those establishing animal colonies. The importance of the health and physical environment of laboratory animals is given in true perspective with regard to investigators' requirements, and both these chapters contain more concise information than may be found in many handbooks devoted entirely to these subjects.

It is surprising but refreshingly

honest for one of the pioneers of specific pathogen-free (SPF) animals (W. Lane-Petter) to declare that "experience of the use of SPF animals has often been most unsatisfactory". Nutrition has been given a comprehensive coverage and the chapter is factual with a minimum of theoretical ideas. Administration and husbandry form the weakest section in this otherwise excellent book. Animal technician training is exceedingly important but some of the details may soon be out of date as the Institute of Animal Technicians is reorganizing its training schemes.

The final chapter is devoted to information on laboratory animal centres, national and international organizations engaged in laboratory animal science, professional societies, legal requirements and the Littlewood Committee report. A comprehensive list of references, a bibliography of books dealing with laboratory animals, and a subject index complete a worthy publication.

Cass's *Annotated Bibliography* comprises three separate compilations; two are reprinted from *Fed. Proc.*, 19 and 22 (1960 and 1963), and the third is by the US Veterans Administration department. Fundamental information which is difficult to find elsewhere in published form is well presented here. Abstracts are provided with each reference and these are invaluable in so far as they provide brief details of the subject matter.

The references in the first two sections have been well chosen from a wide range of subjects including anatomy, physiology, psychology, disease, anaesthesia and euthanasia. Their potential value is somewhat lessened by the fact that there are few references after 1962. A publication of this nature, however, cannot contain completely up to date references because abstracting and preparation are time consuming. The third section specializes in laboratory animal science whereas the earlier compilations covered a wider and more diverse range of subjects.

The literature on laboratory animals which has been quoted is comparatively recent and includes selections from textbooks, monographs and proceedings of symposia, as well as articles from journals. At the end of each section cross references enable the user to consult related abstracts in other sections so that specific details are not overlooked which would defeat the principal purpose of the bibliography.

Omissions must be accepted because it is impossible to cover adequately everything in a bibliography containing about 5,500 references on a variety of subjects.

Nevertheless, this publication will provide valid information up to 1963 and can be used with Medlar who provides references backdated to 1964. It

is the sort of book that the libraries of teaching and research establishments cannot afford to be without.

GEORGE PORTER

Nature of Water

Water and Aqueous Solutions: Structure, Thermodynamics and Transport Processes. Edited by R. A. Horne. Pp. vii+837. (Wiley Interscience: New York and London, March 1972.) £15.

As the editor of this book states in his introduction, the past ten or fifteen years have seen a remarkable revival of interest in the properties of water and aqueous solutions for reasons connected with recognition of the importance of water in biological systems and with pollution and ecological matters. Simultaneously with the growth of sophisticated science and technology, pollution of the environment, especially water resources, has occurred but only recently has society awakened to the dangers of this situation. One is reminded of Renaissance times when, alongside outstanding growth of culture, art and mercantilism, great cities such as Urbino and Florence tolerated the most unhygienic conditions in public places.

The appearance of this book is therefore both timely and academically welcome. The editor has gone to great pains to assemble nineteen chapters, from well-known authorities in the field, which cover the main areas of contemporary interest in the study of water and aqueous solutions. The book starts off with three chapters on ice followed by two comparative chapters on non-aqueous electrolyte solutions by Padova and on fused salts by Rhodes. Chapters on seawater and on biofluids then follow. The next five chapters are concerned with theoretical treatments of water and aqueous solutions and provide an authoritative account of the present state of knowledge in this field. The contributors are Ben-Naim, Stillinger, Davis, Jarzynski, Kell and Vaslow. Chapter 13 by Millero, with its addendum of data on partial molal volumes, is exceptionally valuable because it contains a wealth of tabulated data, critically appraised. Chapters by Samoilov on residence times of ionic hydration and by Wen on tetraalkylammonium salts, which, by their exceptional behaviour in water, have attracted much attention, are then presented. Ling, on hydration of macromolecules, covers a very important field but the treatment is disappointingly old fashioned. Little consideration is given to electrostatic effects at polyions and polyampholytes and ideas on "solute exclusion" from ion-exchange resins and polarized layers are presented without reference to the importance of electrostatic salting-out

effects. The volume concludes with three chapters on viscosity of water, transport coefficients in electrolyte solutions and aqueous solutions under extreme conditions.

The book is marred by a number of errors which will make the reader wary of other material quoted and which may not be so easily checked without reference to the original literature—for example, tabulations of data. The errors begin in the editor's introduction, where Bernal and Fowler's classical paper is spelled out in the text as appearing in the *Journal of Physical Chemistry*⁶; in the reference list, we find, with increasing surprise, that entry 6 is quoted as a non-existent "*Journal of American Physics*, Vol. 1, 1933". The correct reference is, of course, *J. Chem. Phys.*, Vol. 1, a vintage issue, containing, besides Bernal and Fowler's paper, many other contributions outstanding at that time. These incorrect quotations can hardly be printers' errors. On pages 77 and 105 we find reference to Watson-Tobin (Watts-Tobin), while on page 78 "thin" wires 0.45 cm thick are referred to. The correct size reported in the original paper is 0.045 cm. Also, on page 93, the reader concerned with quantitative accuracy may be surprised to find that 30 V is equivalent to 70 kcal mol⁻¹, the correct figure being, of course, about 700 kcal mol⁻¹. Similarly, in the chapter on nonaqueous solutions, the reader will be amused to read on page 143 about the "impaired" electron, an error the author might have been excused from making had this part of the chapter been concerned with the alcoholic solutions referred to on page 118.

While the historical aspects of the field are well covered, particularly in remarks by the editor, a certain myopia must have been suffered by a number of the contributors for failing to quote the seminal paper in which the first thermodynamic evidence for "water structure" effects (a central concept in modern work) in ionization phenomena was demonstrated. The work of Everett and Wynne-Jones (1939–41) on anomalous entropy and heat capacity changes antedates that of Frank and Evans (1945) by 4–6 years. Other important early work on ionization in water by Wynne-Jones is not quoted in the entire volume.

Readers will be reminded of that curiously titled but excellent early book by Dorsey, *The Properties of Ordinary Water Substance*. This new volume goes a long way to demonstrate how extraordinary, in fact, is "water substance". In its up-to-date and thorough coverage of the field, the volume is to be strongly recommended to all chemists, physicists and biologists who are concerned with experiments in this most common, yet unusual, medium.

B. E. CONWAY

Sixth Form Chemistry

ICI Publications for Schools: Sixth Form Topics. Edited by S. M. Neal and J. J. Thompson. General Editor R. A. Finch. *Catalysts*. Pp. 15. *Colloids*. Pp. 14. *Colour Chemistry*. Pp. 19. *Fertilizers*. Pp. 15. *Polymers 1: Long Chain Molecules*. Pp. 11. *Polymers 2: Synthetic Fibres*. Pp. 14. *Polymers 3: Plastics*. Pp. 15. *Spectroscopy*. Pp. 15+20 spectra. (Published by Education Section, ICI Ltd; The Kynoch Press: Thames House, North Millbank, London SW1.) £1 for the set of eight titles.

BOB FINCH is ICI's Schools Liaison Officer, and a specialist in ideas which are not only obviously brilliant but also brilliantly obvious. A former chemistry teacher himself, he saw the need for teaching aids generated by industry and teachers acting in partnership—aids which would be authoritative, readable, up-to-date, and at the same time cheap and immediately useful. A team of thirty-one distinguished teachers, teachers of teachers, and ICI staff all gathered at the University of York in the autumn of last year, and these booklets are largely the result of those three hectic days. The booklets come in sets, all eight titles together in a plastic envelope. Each booklet is punched for filing, ready to form the basis of a collection of material about the topic in question.

Finch's attitude is that he wants the stuff used: burnt full of acid holes and destroyed in two years. ICI has borne the entire cost of generating the material and the excellent price of £1 must be heavily subsidized. I have no doubt that ICI, in producing these booklets, has already performed a great service to school chemistry teaching, and I fervently hope that the series will continue and expand. All schools and colleges dealing in sixth form chemistry ought to have the material to hand.

As would be expected from the composition of the writing teams, the material is generally pitched at the right level. There are many good experiments, with plenty of scope for project work, and some useful exercises involving economic and other factors.

But along with the praise I must record some faint damns. A deadline, as Dr Johnson might have observed, concentrates the mind wonderfully; but, particularly if a team is involved, it can often result in a distinct lumpiness of style. It has also resulted, for all the conscientious labours of the editors, in an irritating number of misprints, mislabellings and doubtful statements. Some of the art work, especially the drawings of molecular structures, is very poor. ICI methods and products are perhaps rather over-emphasized.

This may seem reasonable enough to the producers, but my experience of the consumers leads me to believe that any drum-beating is usually counter-productive.

One can say of most books and material of this kind that the second edition will be better than the first, and this would be true here. But it will probably be another generation of sixth formers before the next edition appears, so if you are a teacher of chemistry at sixth form or college level my firm recommendation is to buy now, while stocks last. And make sure the stuff is used.

MARTYN BERRY

Transplantation

The Immunobiology of Transplantation. By Rupert Billingham and Willy Silvers. Pp xiii+209. (Prentice Hall: Englewood Cliffs, New Jersey, July 1971.) \$9.75 cloth; \$4.95 paper.

THIS slim book will fill the long-empty space on the library shelf waiting for a brief introduction to the laboratory science of transplantation immunology. While the antibody mediated reactions have had a generous share of standard textbooks, cell-mediated immunology has been poorly served, a curious omission in view of the eminence and erudition of the workers in this field. In this book, the two authors who have been closely associated with many of the great advances in immunology are to be thanked for producing a simple, beautifully illustrated account of their subject. Here we find, for instance, a simple account of the mysteries of the H2 antigen system in mice, the theory and uses of the graft-versus-host reaction, and the uses of the mixed lymphocyte reaction. Throughout there is a welcome emphasis on the work transplantation in rodents, which has provided so many fundamental concepts of immunology and continues to provide challenging new phenomena. The historical aspects of the development of transplantation immunology, and the authors' enthusiasm for showing the evolution of modern concepts is much in evidence. This approach, however, leads to a lack of balance in the book: space is found to describe in detail the early tumour grafting work which led to the concept of transplantation antigens, but no account is given of the fundamental division of "T" and "B" lymphocytes. There is also an interesting and detailed account of the now superseded normal lymphocyte transfer reaction, but not of enhancing antibodies as mediators of non-reactivity in many systems other than tumour growth. Nevertheless this is a long awaited and useful book.

D. HAMILTON

Obituary

Professor F. V. Hunt

A LEADING world authority on acoustical engineering, Professor F. V. Hunt died suddenly on April 20, 1972, during the Spring Meeting of the American Acoustical Society at Buffalo. He had been ill intermittently for the past six years but he still retained his effervescent spirit and even on the night of his death had participated fully in some lively discussions.

Born in Barnesville, Ohio, in 1905, Ted Hunt entered Ohio University in 1921 at the age of 16 and, following graduation in the summer of 1925, he started his lifelong interest in automobile touring by selling his silver flute to purchase a Ford car. These yearly travels were depicted in a fascinating manner on greeting cards to his many friends at Christmas. Just prior to his PhD award at Harvard in 1934, for a thesis on frequency modulated signals in reverberation measurements, he married Katherine Buckingham whose

father was a Bureau of Standards physicist and was the originator of the π -theorem of dimensional analysis. By 1941 Hunt had become Associate Professor of Physics and Communication Engineering at Harvard Underwater Sound Laboratory (HUSL) and in 1942 he became director of the laboratory. The laboratory's objectives were to improve existing equipment and to design new equipment for submarine detection and localization. At the peak of activity in 1944 the laboratory staff reached a total of 450.

The most important products of HUSL were the scanning sonar and the acoustic torpedo, the latter device being probably the first guided missile, and remarkably it was designed and in operation within eighteen months. An interesting by-product was the acoustic "beeper" which could be attached to a torpedo during proof testing and helped locate torpedoes which had become wayward in action.

In 1946 he became the Gordon McKay Professor of Applied Physics,

and he also held the Rumford chair in the department of physics from 1953.

Hunt was dedicated to his field of study and for over thirty years did not miss a single meeting of the American Acoustical Society. He was the recipient of many honours and from his country he received the Presidential Medal of Merit and the Navy Distinguished Public Service Medal, from the American Acoustical Society the Pioneers of Underwater Acoustics Medal and the Society Gold Medal (he was President of the AAS in 1951), and from the Audio Engineering Society the Potts Memorial Award. His greatest satisfaction, however, stemmed from the great affection in which he was held by his many graduate students, who are living evidence of the high academic standard of their training.

After his retirement two years ago Hunt continued work as a research associate at the Marine Physical Laboratory of the Scripps Institution of Oceanology. He will be greatly missed by his family and his friends.

Announcements

University News

Professor Clement Camford has been appointed a Pro-Vice-Chancellor at the University of Liverpool.

International Meetings

September 3-9, **IXth International Congress of Nutrition**, Mexico City (IX Congreso Internacional de Nutrición, PO Box 22-112, México, D.F. México).

September 4-15, **Science and Technology of Electronic Materials**, Lake Como (Professor U. Colombo, Director, Strategic Planning, Montecatini Edison S.p.A., Largo Donegani, 2, 20121 Milan).

September 5-7, **International Symposium of the Occupational Safety and Health of Young Workers**, Belgrade (Occupational Safety and Health Branch, International Labour Office, 1211 Geneva 22).

September 5-7, **Recent Mathematical Developments in Control**, Bath (Secretary, Institute of Mathematics and Its Applications, Maitland House, Warrior Square, Southend-on-Sea, Essex SS1 2JY).

September 5-8, **Plant Cell Protoplasts and their Molecular Biological Implications**, Tübingen (Professor Georg Melchers, D 74 Tübingen, Corrensstr. 41, Max-Planck-Institut für Biologie).

September 10-23, **Summer School in Theoretical Chemistry**, Oxford (Professor C. A. Coulson, Mathematical Institute, 24-29 St Giles, Oxford OX1 3LB).

September 12-15, **VIIIth International Federation of Societies of Cosmetic Chemists**, Congress, Hamburg (Dr Herbert P. Fiedler, D-62 Wiesbaden, Lantzstrasse 4, Germany).

September 13-15, **VIIIth International Symposium on Chromatography and Electrophoresis**, Brussels (Secretariat of the Belgian Society of Pharmaceutical Sciences, 11 rue Archimède, 1040 Brussels).

September 15-17, **Social Responsibility and Education in Physics**, Leeds (Meetings Officer, Institute of Physics, 47 Belgrave Square, London, SW1X 8QX).

September 20-21, **Offshore Engineering**, Edinburgh (Arthur C. Gardiner, Director of Unilink, Heriot-Watt University, 79 Grassmarket, Edinburgh EH1 2HJ).

September 20-27, **Workshop on Electromagnetic Induction**, Edinburgh (Dr B. A. Hobbs, Department of Geophysics, University of Edinburgh, 6 South Oswald Road, Edinburgh EH9 2HX).

September 25-26, **Electro-Optic Systems in Flow Measurement**, Southampton (Clive Greated, University of Southampton, Department of Mathematics, Southampton SO9 5NH).

September 25-27, **Groundwater Pollution**, Reading (Water Research Association, Medmenham, Marlow, Buckinghamshire SL7 2HD).

September 29, **Amino-sugar Synthesis and Reactions**, London (Dr N. R. Williams, Chemistry Department, Birkbeck College, Malet Street, London WC1E 7HX).

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

List of University Institutions in the Commonwealth. Sixteenth edition. Pp. 26. (London: The Association of Commonwealth Universities, 1972.) [37]

Forestry Policy. Pp. 15. (London: HMSO, 1972.) 18p. net. [37]

The Committee of Vice-Chancellors and Principals of the Universities of the United Kingdom. A Compendium of University Entrance Requirements for First Degree Courses in the United Kingdom in 1973-74, excluding Degree Courses for External Students. Pp. 307. (London: The Association of Commonwealth Universities, 1972.) £1.40. [37]

Fabian Research Series. No. 303: Education for a Multi-Racial Britain. By Felicity Bolton and Jennie Laishley. Pp. 20. 20p. No. 304: First Schools of the Future. By Tessa Blackstone. Pp. 24. 25p. (London: Fabian Society, 1972.) [47]

The University of Nottingham. General Prospectus 1973-4. Pp. 48. (Nottingham: The University, 1972.) [47]

Smith Kline and French Foundation. Ninth Annual Report 1971. Pp. 6. (Welwyn Garden City, Herts: Smith Kline and French Foundation, 1972.) [57]

Republic of Ireland. Sea and Inland Fisheries Report for 1970. Pp. 67. (Dublin: Stationery Office, 1972. Obtainable from Government Publications Sale Office, GPO Arcade.) 20p. [57]

Building Research Station Digest, No. 143: Sound Insulation: Basic Principles. Pp. 8. (London: HMSO, 1972.) 5p. [57]

The West of Scotland Agricultural College: Grassland Husbandry Department. Current Experimental Programme, No. 15, April 1972. Pp. 37. Advisory Leaflet No. 86: Recommended Varieties of Herbage Plants. Pp. 2. Experimental Records, No. 26: Comparison of Productivity of Perennial Ryegrass Varieties (Series VI, VII and VIII). By I. V. Hunt, J. Frame and R. D. Harkess. Pp. 39. No. 27: Age Effects on Yields of 4 Grass Species and their Response to Fertilizer Nitrogen. By I. V. Hunt. Pp. 62. No. 28: Potash and Phosphate Requirements of a Perennial Ryegrass Sward Managed for High Yields. By I. V. Hunt, F. Frame and R. D. Harkess. Pp. 31. (Auchincruive, Ayr: The West of Scotland Agricultural College, 1971 and 1972.) [57]

Beecham Group Limited. Annual Report for the year ended 31st March 1972. Pp. 23. (Brentford, Middlesex: Beecham Group Limited, 1972.) [57]

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Pesticides in the Modern World. (A symposium prepared by members of the Co-operative Programme of Agro-Allied Industries with FAO and other United Nations Organizations, 1972.) Pp. 60. (London: The British Agrochemicals Association, 93 Victoria Embankment, 1972.) gratis. [67]

Thermal Analysis Abstracts. Editor-in-Chief: Dr. J. P. Redfern. Price £40; \$98; DM 360 per annum, including binder and cumulative subject index. (London: Heyden and Son; Rheine/Westf: Heyden and Sohn, GmbH, 1972.) [67]

Science Research Council. The Work of the Rutherford Laboratory in 1971. Edited by J. R. Smith and F. M. Telling. (RHEL/R 243). Pp. 223. (Chilton, Didcot: Rutherford High Energy Laboratory, 1972. Available from HMSO.) £1 net. [67]

National Vegetable Research Station. Annual Report for 1971. Pp. 100+8 plates. (Wellesbourne, Warwick: National Vegetable Research Station, 1972.) 65p. [77]

Department of Health and Social Security; Scottish Home and Health Department; Welsh Office. Hepatitis and the Treatment of Chronic Renal Failure: Report of the Advisory Group 1970-1972. Pp. 55. (London: Department of Health and Social Security, 1972.) [77]

Royal Aircraft Establishment, Farnborough. Index to the International Congresses on High Speed Photography, 1952-1970. Compiled by Jill Wadsworth and M. W. Glover. Pp. 158. (Farnborough: Central Unit for Scientific Photography, Royal Aircraft Establishment, 1972.) [77]

Other Countries

Berichte des Deutschen Wetterdienstes. Nr. 127 (Band 17): Synoptik und Energetik der Hamburger Sturmflutwetterlage vom Februar 1962. Von F. Defant, H. Fechner und P. Speth. Pp. 85. Nr. 128 (Band 17): Lokalklimatische Studien im Odenwald. Von Fritz Schelle. Pp. 38. (Offenbach a.M.: Selbstverlag des Deutschen Wetterdienstes, 1972.) [206]

World Health Organization. Technical Report Series, No. 495: Opiates and their Alternatives for Pain and Cough Relief—Report of a WHO Scientific Group. Pp. 19. (Geneva: WHO; London: HMSO, 1972.) 3 Sw. francs; 30p; 75 cents. [226]

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US Department of the Interior: Geological Survey. Professional Paper 724-C: Geochemistry of Diagenetic Dolomites in Miocene Marine Formations of California and Oregon. By K. Murata, Irving Friedman and Marcelyn Cremer. Pp. iii+12. (Washington, DC: Government Printing Office, 1972.) 30 cents. [236]

Fisheries Research Board of Canada. Technical Report No. 295: Design and Performance of TURP—a Diver Controlled Towed Underwater Research Plane. By T. J. Foulkes and D. J. Scarratt. Pp. 11. (St. Andrews, NB: Fisheries Research Board of Canada, Biological Station, 1972.) [236]

New Zealand: Department of Health. Fallout from Nuclear Weapons Tests Conducted by France in the South Pacific from June to August 1971, and Comparisons with Previous Test Series. Compiled by L. P. Gregory. Pp. 41. (Christchurch, NZ: National Radiation Laboratory, 1972.) [236]

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Biominalisation—Research Reports. Band 4. Pp. 100. (Stuttgart and New York: F. K. Schattauer Verlag, 1972.) [266]

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Australia: Commonwealth Scientific and Industrial Research Organization. Division of Fisheries and Oceanography Circular No. 6: Essays in Fisheries Science. By G. L. Kesteven, T. W. Burdon, R. R. Ingpen and C. R. Williams. Pp. 107. (Melbourne: CSIRO, 1971.) [266]

Veröffentlichungen der Schweizerischen Meteorologischen Zentralanstalt/Publications de l'Institut Suisse de Météorologie. No. 23: Abgrenzung von Wetterlagen im Zentralen Alpenraum. Von Walter Kirchhofer. Pp. 69. No. 24: Le Climat, Élément du Plan d'Aménagement/The Climate as an Element of the Land Management. Par B. Primault. Pp. 27. No. 25: Die Verschiedenen Messverfahren zur Bestimmung der Strahlungssintensität mit dem Kompensations-pyreheliometer und die Entwicklung eines Verbesserten Modells. Von C. Fröhlich und H. Wierzejewski. Pp. 31. (Zürich: Schweiz Meteorologische Zentralanstalt, 1971 and 1972.) [266]

US Department of the Interior: Geological Survey. Bulletin 1354-D: Revision of Stratigraphic Names for Some Eocene Formations in Santa Barbara and Ventura Counties, California. By J. G. Vedder. Pp. 12. 10 cents. Water-Supply Paper 1912: Surface Water Supply of the United States, 1961-65. Part 4: St. Lawrence River Basin. Vol. 2: St. Lawrence River Basin Below Lake Huron. Pp. ix+734. (Washington, DC: Government Printing Office, 1971 and 1972.) [276]

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Indian Forest Bulletin No. 259 (New Series, Wood Seasoning): Variation of Specific Gravity and Tangential Shrinkage in the Wall Thickness of Bamboo (*Dendrocalamus strictus*) and its Possible Influence on the Trend of the Shrinkage-Moisture Content Characteristic. By S. N. Sharma and M. L. Mehra. Pp. 6. (Delhi: Manager of Publications, 1970.) Rs. 1.70; 20p; \$0.62. [337]

Australia: Commonwealth Scientific and Industrial Research Organization. Division of Fisheries and Oceanography Technical Paper No. 32: Geopotential Topographies and Currents Off West Australia, 1965-69. By B. V. Hamon. Pp. 11. (Melbourne: CSIRO, 1972.) [337]

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